Trimodal Gadolinium-Gold Microcapsules Containing Pancreatic Islet Cells Restore Normoglycemia in Diabetic Mice and Can Be Tracked by Using US, CT, and Positive-Contrast MR Imaging¹

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Purpose:

To develop microcapsules that immunoprotect pancreatic islet cells for treatment of type I diabetes and enable multimodal cellular imaging of transplanted islet cells.

Materials and Methods:

All animal experiments were approved by the institutional animal care and use committee. Gold nanoparticles functionalized with DTDTPA (dithiolated diethylenetriamine-pentaacetic acid):gadolinium chelates (GG) were coencapsulated with pancreatic islet cells by using protamine sulfate as a clinical-grade alginate cross linker. Conventional poly-L-lysine-cross-linked microcapsules and unencapsulated islets were included as controls. The viability and glucose responsiveness of islet cells were assessed in vitro, and in vivo insulin (C-peptide) secretion was monitored for 6 weeks in (streptozotocin-induced) diabetic mice with ($n = 7$) or without ($n = 8$) intraabdominally engrafted islet cells. Five nondiabetic mice were included as controls. Differences between samples were calculated by using a nonparametric Wilcoxon Mann-Whitney method. To adjust for multiple comparisons, a significance level of $P < .01$ was chosen. Generalized estimating equations were used to model cell function over time. Three mice with engrafted capsules were imaged in vivo with high-field-strength (9.4-T) magnetic resonance (MR) imaging, micro-computed tomography (CT), and 40-MHz ultrasonography (US).

Results:

Encapsulated human pancreatic islets were functional in vitro for at least 2 weeks after encapsulation. Blood glucose levels in the diabetic mice transplanted with GG-labeled encapsulated mouse β TC6 insulinoma cells returned to normal within 1 week after transplantation, and normoglycemia was sustained for at least 6 weeks without the use of immunosuppressive drugs. GG microcapsules could be readily visualized with positive-contrast high-field-strength MR imaging, micro-CT, and US both in vitro and in vivo.

Conclusion:

Cell encapsulation with GG provides a means of trimodal noninvasive tracking of engrafted cells.

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In type I diabetes mellitus, the body is unable to produce insulin owing to an autoimmune response against pancreatic islet cells. Without treatment, patients suffer from serious complications, including cardiovascular disease, neuropathy, retinopathy, and nephropathy. Regular insulin administration is the current preferred treatment for type I diabetes, but it is often difficult to properly synchronize the insulin injections with blood glucose levels. For patients with type I diabetes, transplantation of human cadaveric islets enables a precise temporal regulation of insulin that is not achievable with exogenous insulin injection. Findings in multiinstitutional trials confirmed that the results obtained with the so-called Edmonton protocol (1,2) could be reproduced elsewhere, with an impressive insulin-independent rate of 90% (3). However, the success rates with this protocol were found to vary, with some rates as low as 23% (4). Because the underlying differences that cause these substantial variations are poorly understood, there is a need for noninvasive monitoring of the fate of islets after their transplantation (5–8). In particular, a more sensitive means of correlating the long-term function of individual islets with the anatomic location and route of transplantation, as well as a method for assessing successful engraftment versus immunorejection, is necessary (9–15). Human islet cells have been labeled with a magnetic resonance (MR) contrast agent (ferucarbotran, Resovist; Bayer Schering Pharma, Berlin, Germany) and transplanted into patients with type I diabetes to evaluate

the persistence of the MR signal intensity of engrafted islets (16).

To prevent islet rejection, patient recipients currently require immunosuppressive therapy, which increases their chance of infection and cancer, and the most commonly used drugs are toxic to pancreatic beta cells. Immunoisolation techniques such as microencapsulation have been shown to have considerable potential for preventing immune-mediated cell destruction without the use of immunosuppressive drugs (17). Microencapsulation provides a semi-permeable membrane that prevents the passage of antibodies but allows the passage of cell-derived factors, including insulin. Given that clinical trials (18,19) and nonhuman primate studies (20–23) of engrafted encapsulated islets have been performed, the development of a clinically applicable method that enables noninvasive monitoring of the real-time delivery, tissue engraftment, and persistence of capsule integrity is highly desirable (24). To this end, capsules labeled with barium or bismuth sulfate (25), superparamagnetic iron oxide (26,27) perfluorocarbons (28), or a combination of superparamagnetic iron oxide and gold nanoparticles (29) have been developed that allow monitoring of engraftment with MR imaging, fluoroscopy or computed tomography (CT), and ultrasonography (US). However, microcapsules labeled with a positive MR contrast agent are preferred for better visualization of capsules engrafted into a transplantation site that appears dark on conventional MR images, such as the liver. The liver is currently considered the most suitable site for pancreatic cell engraftment owing to its high perfusion.

We hypothesized that gold nanoparticles functionalized with DTDTPA (dithio-

lated diethylenetriaminepentaacetic acid); gadolinium chelates (GG) could serve as a contrast agent for three imaging modalities: MR imaging (particularly positive-contrast MR imaging), CT, and US. Each of these imaging modalities has its own advantages and limitations. MR imaging provides excellent soft tissue contrast and spatial resolution and therefore appears to be the most appropriate for accurately localizing engrafted islets. However, MR imaging procedures are relatively costly compared with fluoroscopy, CT, and US, especially when interventional procedures are being used to inject therapeutic cells. Also, from a technical perspective, few centers are set up for MR-guided injections. On the other hand, injections performed under fluoroscopic and US guidance are common clinical practice. Although fluoroscopy is less sensitive for contrast agents and labeled cells, this imaging process is fast and can be easily performed in real time (30). Unlike MR-guided injections, injections performed under fluoroscopic, CT, or US guidance can also be performed in patients with non-MR-compatible implants such as

Advances in Knowledge

- Capsules labeled with gadolinium-gold nanoparticles could be visualized by using MR, CT, and US imaging, combining the strengths and versatility of each of these modalities within one formulation.
- Intraabdominal transplantation of cells coencapsulated with gadolinium-gold nanoparticles restored normoglycemia in diabetic mice for at least 6–7 weeks.

Implication for Patient Care

- In patients with type I diabetes, transplantation of pancreatic cells coencapsulated with gadolinium-gold nanoparticles may enable tracking of engrafted encapsulated cells with conventional imaging technologies.

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Abbreviations:

APLLA = alginate-poly-L-lysine-alginate
 APSA = alginate-protamine sulfate-alginate
 DTDTPA = dithiolated diethylenetriaminepentaacetic acid
 Gd³⁺ = cationic gadolinium ion
 GG = gold nanoparticles functionalized with
 DTDTPA: gadolinium chelates

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cardiac pacemakers. For transplantation of pancreatic islets into the liver, intra-portal infusion is typically performed under CT guidance by using a fluoroscopy-compatible catheter. US is the least sensitive imaging modality and is unable to generate a whole-body image; however, it is fast, safe, and the least expensive, and it exists in the form of a bedside (portable) clinical imaging unit that is widely available. Thus, our overall objective was to develop microcapsules that immunoprotect pancreatic islet cells for treatment of type I diabetes and enable multimodal cellular imaging of transplanted islet cells.

Materials and Methods

GG Synthesis and Microcapsule Labeling

GG was synthesized as previously described (31,32) (Appendix E1 [online]). Two types of alginate microcapsules were prepared: conventional alginate-poly-L-lysine-alginate (APLLA) capsules (25,26,33) and new alginate-protamine sulfate-alginate (APSA) capsules (Fig 1, A; Appendix E1 [online]). To prepare labeled capsules, GG nanoparticles were cosuspended with human islets in low-viscosity high-guluronate alginate before bead formation. The encapsulated gold concentration was measured by using inductively coupled plasma mass spectrometry (Microbac Laboratories, Baltimore, Md). The molar ratio of chelated gadolinium to gold was approximately 1:9.

Assessment of Cell Viability and Function in Vitro

The viability of the encapsulated mouse β TC-6 insulinoma cells was determined 1 day after the encapsulation (Appendix E1 [online]). For assessment of insulin production, the GG-labeled and unlabeled capsules containing an average of one human islet per capsule were cultured in a six-well plate with 300 capsules per well. Equal numbers of unencapsulated (naked) islets were cultured in parallel for comparison. The culture medium was changed and collected every 3 days. The level of C-peptide

secreted from the encapsulated and naked human islets was determined by using a C-peptide enzyme-linked immunosorbent assay kit (Alpco Diagnostics, Salem, NH). The experiment for each capsule type and naked islets was repeated for a total of four samples. The total number of samples was limited by the number of human islets—obtained from fresh human cadavers—available at the time of the experiment. A glucose stimulation test was performed (Appendix E1 [online]), with the results presented as the glucose responsiveness index—that is, the concentration of human C-peptide in the high-glucose medium divided by the concentration of human C-peptide in the low-glucose medium.

Animal Studies

The animal studies were approved by the animal care and use committee of The Johns Hopkins University School of Medicine. Fifteen C57BL/6J mice with streptozotocin-induced diabetes and five normal control C57BL/6J mice were obtained commercially (Jackson Laboratory, Bar Harbor, Me). A mouse was deemed to be diabetic if its non-fasting blood glucose level was higher than 300 mg/dL. Four weeks after the streptozotocin injection, approximately 6000 APSA + GG capsules containing a total of 7.5×10^6 mouse β TC-6 insulinoma cells were transplanted intraperitoneally into seven diabetic mice on the same day as the capsule preparation. Blood glucose levels were measured by using a glucometer (Accu-Check Aviva; Roche Diagnostics, Indianapolis, Ind) on the day the animals arrived from the vendor, immediately before capsule transplantation, every 2–3 days for the first 3 weeks after the transplantation, and once a week thereafter. Eight nontreated diabetic mice and five healthy mice served as controls. For MR, CT, and US imaging, 3000–4000 empty APSA + GG microcapsules were subcutaneously injected into the abdomen of three healthy mice immediately after capsule synthesis. The three mice were imaged with micro-CT and US 1 day after capsule engraftment. These

same mice were then imaged with MR imaging 2 days after engraftment.

Imaging

MR imaging of phantoms (100 empty APSA + GG microcapsules in saline) and mice was performed by using a 9.4-T horizontal bore magnet (Bruker BioSpin, Karlsruhe, Germany) (Appendix E1 [online]). Micro-CT of the phantoms and mice was performed by using an X-SPECT Gamma Medica imager (Gamma Medica-Ideas, Northridge, Calif) with tube settings of 75.16 kV and 240.3 μ A, a 64-mm detector setting, and 512 projections. For US, the phantoms and mice were imaged by using a 40-MHz Vevo 660 scanner (VisualSonics, Toronto, Ontario, Canada) with an RMV-40C scanning head. The settings used to perform US were a master gain of 14 dB and a field of view of 20×20 mm for the microcapsule phantoms in saline, and a master gain of 11 dB and a field of view of 8×8 mm for the mice.

Statistical Analysis

Differences between experimental groups were calculated by using a nonparametric Wilcoxon Mann-Whitney method. To adjust for multiple comparisons, the significance level was selected as $P < .01$. A generalized estimating equations model was fitted to analyze the longitudinal measurements of in vitro human C-peptide levels and in vivo mouse blood glucose levels over time. Estimated differences were calculated on the basis of the generalized estimating equations model. The predictors in the model included time (in days), sample group, and an interaction term between time and sample group. SAS, version 9.2 (SAS Institute, Cary, NC), software was used for statistical analysis. A post hoc power analysis was performed by using a two-sample *t* test (differences) and PASS 11 software (NCSS Statistical and Power Analysis Software, Kaysville, Utah).

Results

Properties of GG and GG Microcapsules

The average diameter of the GG nanoparticles was 2.0–2.5 nm, with a single

Figure 1

Figure 1: A, Three-dimensional scheme of APSA microcapsule containing GG (APSA + GG). The semipermeable microcapsule allows diffusion of oxygen, nutrients, glucose, and insulin, while passage of immune cells and antibodies is blocked. B, C, Light microscopic images of APSA + GG microcapsule 1 hour (B) and 2 days (C) after synthesis. D, Human pancreatic islet inside APSA + GG microcapsule. E, Fluorescence microscopic image shows viability staining of mouse insulinoma β TC-6 cells inside APSA + GG microcapsule. Green (fluorescein diacetate stain) = live cells, red (propidium iodide stain) = dead cells. Scale bars = 200 μ m.

particle containing 50 cationic gadolinium ion (Gd^{3+}) chelates (31,32) (Appendix E1 [online]). The GG microcapsules had a mean diameter of $542 \mu m \pm 19$ and contained, on average, one human islet per capsule (Fig 1, B–D). The nanoparticles were homogeneously distributed inside the capsules for up to 2 days after the synthesis (Fig 1, B). Afterward, the nanoparticles redistributed and aggregated inside the capsules (Fig 1, C) (Appendix E1 [online]). Inductively coupled plasma mass spectrometry revealed that each capsule contained 1 ng of gold and approximately 87.7 pg of Gd^{3+} . The GG microcapsules were stable for at least 1 year in physiologic saline in vitro, without perceivable changes in capsule size and morphology and leakage of nanoparticles (Appendix E1 [online]).

Encapsulated Cell Function in Vitro

In Figure 1, E, a representative US image shows viability staining of mouse β TC-6 insulinoma cells housed in an APSA + GG microcapsule. The relative viabilities (in percentages) of the mouse β TC-6 insulinoma cells inside APLLA – GG, APSA – GG, and APSA + GG capsules are presented in Figure 2, A. The viability of cells housed in the APSA – GG ($P < .0001$) and APSA + GG ($P = .008$) microcapsules was significantly higher than that of cells housed in the APLLA – GG capsules. Comparison between the APSA – GG and APSA + GG capsule groups yielded $P = .314$. Post hoc power analysis of the APSA – GG and APSA + GG capsule groups revealed 11% power to detect a difference between the two groups.

The levels of C-peptide secretion of the encapsulated human islets and naked islets in culture are shown in Figure 3. Over time there was a decrease in C-peptide level in all three capsule groups, as human pancreatic islets do not survive long in culture (34). In addition, the decrease was significantly greater in the APSA + GG group than in the naked islet group (estimated difference, 38.46; $P < .0001$) and in the APSA – GG group (estimated difference, 39.56; $P < .0001$). However, there was no significant difference in the rate of decrease between the APSA – GG and naked islet group (estimated difference, –1.10; $P = .89$).

Human islets inside APSA + GG and APSA-GG microcapsules secreted C-peptide for at least 15 days in vitro. The C-peptide secretion levels of islets inside the APSA + GG and APSA – GG microcapsules were not significantly different from the secretion levels of naked islets for all time points ($P = .029$ to $P = .886$ for all time points). The in vitro glucose responsiveness of islets inside APSA – GG ($P = .07$) and APSA + GG ($P = .07$) capsules were not significantly different from the glucose responsiveness of naked islets (Fig 2, B).

In Vivo Cell Function

The blood glucose levels of the diabetic mice implanted with GG capsules containing mouse β TC-6 insulinoma cells returned to the levels of healthy mice 7 days after transplantation and remained normoglycemic for at least 6 weeks (Fig 4). In contrast, all of the nontreated diabetic mice remained hyperglycemic. At baseline (day 7), there was a significant difference in blood glucose levels between the nontreated and treated diabetic mice (estimated difference, 304.40; $P < .0001$) and between the nontreated diabetic mice and the healthy mice (estimated difference, 315.95; $P < .0001$) (Table E1 [online]). However, the difference in blood glucose levels between the healthy mice and the treated diabetic animals was not significant (estimated difference, –11.55; $P = .57$). There was no significant change in blood glucose levels over time after

Figure 2

Figure 2: A, Box and whisker plots show viability of mouse β TC-6 insulinoma cells inside unlabeled APLLA capsules (APLLA — GG, $n = 14$), unlabeled APSA capsules (APSA — GG, $n = 14$), and APSA capsules labeled with GG (APSA + GG, $n = 10$) 1 day after encapsulation. B, Box and whisker plots show in vitro glucose responsiveness (GR) indexes of naked human islets ($n = 3$), human islets inside APSA — GG capsules ($n = 3$), and APSA + GG capsules ($n = 3$) 2 days after encapsulation. Glucose responsiveness index is human C-peptide concentration in high-glucose medium divided by human C-peptide concentration in low-glucose medium. Median (blue lines) and mean (*) values are shown. P values were calculated by using Wilcoxon Mann-Whitney test.

Figure 3

Figure 3: Box and whisker plots show in vitro human C-peptide secretion levels of naked human islets ($n = 4$), and of human islets inside APSA — GG ($n = 4$) and APSA + GG ($n = 4$) microcapsules. Median (blue lines) and mean (*) values are shown. P values were calculated by using Wilcoxon Mann-Whitney test.

baseline (day 7) (Table E1 [online]). Moreover, there was no significant difference in the rate of change over time between any of the mouse groups: The treated diabetic mice maintained a healthy blood glucose level for 6–7 weeks after treatment.

Trimodal Imaging Studies

The MR imaging appearances of the capsules as hyperintense on the T1-weighted MR images and as hypointense on the T2*-weighted images are shown in Figure 5. The resolution on the micro-CT images was lower, but a cluster of

100 microcapsules in saline could still be clearly visualized as bright signals on these scans (Fig 5, C). GG capsules were also visible on the US images (Fig 5, D), but the unlabeled capsules also showed US contrast (Fig 5, H). However, the acoustic reflection of the GG

Figure 4

Figure 4: In vivo functionality of mouse insulinoma β TC-6 cells inside APSA + GG microcapsules. Tx = transplantation of capsules at day 0. Data represent blood glucose levels in diabetic mice with capsules engrafted into peritoneal cavity (circles, seven mice), nontreated diabetic mice (squares, eight mice), and healthy mice (triangles, five mice). Mice with blood glucose levels higher than 300 mg/dL (horizontal dashed line) were considered diabetic. * = time point when blood glucose levels of treated diabetic mice decreased to normoglycemia.

Figure 5

Figure 5: A, E, T1-weighted and B, F, T2*-weighted 9.4T MR images; C, G, micro-CT images (scales in Hounsfield units); and D, H, 40-MHz US images of APSA + GG (top) and APSA - GG (bottom) microcapsules in saline. Single APSA + GG microcapsules are clearly visualized as hyper- and hypointense at 9.4-T MR imaging.

capsules was much stronger than that of the unlabeled capsules (Appendix E1, Fig E1 [online]). Notably, a signal from a single GG capsule could be visualized in vitro.

Empty GG microcapsules subcutaneously injected into a mouse abdomen were clearly visible as hyperintense sig-

nals on the in vivo T1-weighted MR images (Fig 6, A). GG capsules could not be visualized in vivo on the T2*-weighted images, as the low signal intensity of the peritoneum precluded proper visualization. Clusters of capsules were seen in vivo as bright signals on the micro-CT images (Fig 6, B). Finally, with

US, signals that originated from the GG capsules could be observed in vivo (Fig 6, C).

Discussion

We chose to combine gadolinium and gold in a multimodal contrast agent formulation for labeling alginate microcapsules. Gd^{3+} , when chelated to the appropriate ligand, is the most effective clinically used positive-contrast MR agent by virtue of its seven unpaired electrons, while gold is an electron-dense bioinert material suitable for CT. Gd^{3+} ions were chelated onto gold nanoparticles using a pentetic acid ligand, which is present in the clinical-grade formulation, gadopentetate dimeglumine.

Because it has been previously reported that APLLA capsules may cause fibrosis (35)—possibly as a result of the host tissue's exposure to poly-L-lysine-derived cationic lysine residue that branches out into the outer layer of alginate (18,36)—we decided to use protamine sulfate as a polycation to cross link alginate capsules instead. Protamine sulfate is a clinical-grade antiheparin drug that has been reported to have less toxicity than other cationic transfection agents (37) and has been used in conjunction with ferumoxides to render cells magnetic for MR imaging cell-tracking studies (38). The viability of mouse β TC-6 insulinoma cells inside APSA + GG ($P = .008$) and APSA - GG ($P < .0001$) capsules was significantly higher than the viability of such cells inside conventional APLLA capsules. The viability of β TC-6 cells inside APSA - GG versus APSA + GG capsules was not significantly different ($P = .314$), indicating that the GG had no adverse effects on the encapsulated cells.

The encapsulated human islets preserved their biologic function, as indicated by their glucose responsiveness and C-peptide secretion levels over 15 days in culture. Unencapsulated naked pancreatic islets quickly break down into individual cells (34). In our current studies, the hydrogel matrix of the capsules provided a three-dimensional environment that was beneficial for embedding islets and preserving their overall structure.

Figure 6: A, Positive-contrast 9.4-T MR image and, B, micro-CT image (scale in Hounsfield units) of APSA + GG microcapsules (arrow) injected subcutaneously into mouse abdomen. C, D, 40-MHz US images of fluid cavity between abdominal skin and parietal peritoneum of mouse with (C) and without (D) injected APSA + GG microcapsules.

The decrease in human C-peptide levels of islets inside APSA + GG capsules was greater than the decrease in human C-peptide levels of the naked islets and the islets encapsulated in APSA – GG. We hypothesized that the inclusion of GG in the capsules slightly reduced the rate of protein diffusion out of the capsules and therefore decreased the concentration of C-peptide released into the culture media.

We found that the cells transplanted into mice were effectively housed by the APSA + GG microcapsules for up to 6–7 weeks. The diabetic mice received no immunosuppressant drugs throughout treatment. As evident from the longitudinal statistical analysis findings, the mouse insulinoma cells housed inside APSA + GG capsules retained their curative properties in vivo, and diabetic blood glucose levels returned to the normoglycemic state within 1 week after transplantation. The mice that received the APSA + GG microcapsules showed no adverse health effects throughout the 6–7-week postengraftment period.

Paramagnetic gadolinium shortens the longitudinal (T1) and transverse (T2) relaxation times of water protons in tissue (39). The GG capsules had a strikingly bright appearance on the in vitro T1-weighted MR images. Notably, a single GG capsule with high signal intensity could be easily detected in vitro. Single GG capsules also could be seen on the in vitro T2*-weighted MR images, but with conventional hypointense contrast at high magnetic field strength (9.4 T). A cluster of 100 GG capsules could be easily imaged in vitro with micro-CT. Single unlabeled capsules could be detected in vitro with US. This finding was surprising but not unexplainable since microbubbles, which are similar to the capsules that we used, are used as US contrast agents. The US signal was enhanced after encapsulation of the GG.

Naked pancreatic islets—and encapsulated pancreatic islets in particular—require a highly perfused transplantation site for sustained oxygenation of islets. In their native environment, islets in the pancreas have a blood perfusion

rate about 10 times higher than that of cells elsewhere in the body. Therefore, the liver, the largest well-perfused organ in the body, is considered the optimal engraftment site, although other transplantation sites have been considered. In previous studies, human islets coencapsulated with ferumoxides particles (T2-weighted MR contrast agents) were successfully transplanted into the liver of a swine via intraportal infusion (26). In addition, ferucarbotran-labeled naked human islets have been grafted along this route in patients with type I diabetes (16). For the liver and other transplantation sites that have a relatively short T2, a positive-contrast MR signal is preferred for better visualization of transplanted capsules. This was exemplified in our study, in which we transplanted APSA + GG capsules into the peritoneal cavity of mice, which appeared as a strong hypointense background. By using GG as our contrast agent, we were able to clearly visualize hyperintense capsules for immunoisolation of engrafted cells. Barnett et al described formulations that are visible with either hydrogen 1 MR imaging (26) or CT (25) but not both modalities. We demonstrated that APSA + GG microcapsules are visible with MR, CT, and US imaging. While each imaging modality has its own advantages and disadvantages, the use of APSA + GG microcapsules provides a versatile platform for multimodal imaging.

For clinical studies in the human liver, we roughly estimate that approximately 100 000 islets are needed; this is less than the current human dose of 1 million naked islets, given that our islets are immunoprotected and survive much longer. On the basis of our current data—measurements of 1.0 ng of Au³⁺ (gold ion) and 87.7 pg of Gd³⁺ per capsule—this would translate to a total dose of 100 µg of gold and 8.8 µg of gadolinium for a 70-kg individual. There are several factors to consider before translating this technology for human use, including the biocompatibility of our materials, the long-term immunoprotective efficacy of the capsules, the sensitivity of the contrast agent in clinical imaging settings, the retention

capability of the contrast agent, and the number of islets and capsules required to render diabetic patients normoglycemic. The limitations that we encountered in this study were the small sample sizes and the limited time of the animal study follow-up (6–7 weeks). These limitations will be addressed in future studies.

We developed APSA + GG microcapsules for engraftment of pancreatic islet cells. In vitro and in vivo mouse studies revealed the potential of pancreatic cells housed inside APSA + GG microcapsules for treatment of type I diabetes without the need for immunosuppressive therapy. APSA + GG capsules were detectable in vivo with MR, CT, and US imaging and thus provided a versatile means for noninvasively monitoring engrafted capsules in real time. Moreover, to our knowledge, APSA + GG capsules are the first MR-hyperintense microcapsules for improved visualization of capsules transplanted into a hypointense transplantation site such as the abdomen or liver. This GG microencapsulation approach may also be applicable for other forms of cell therapy.

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