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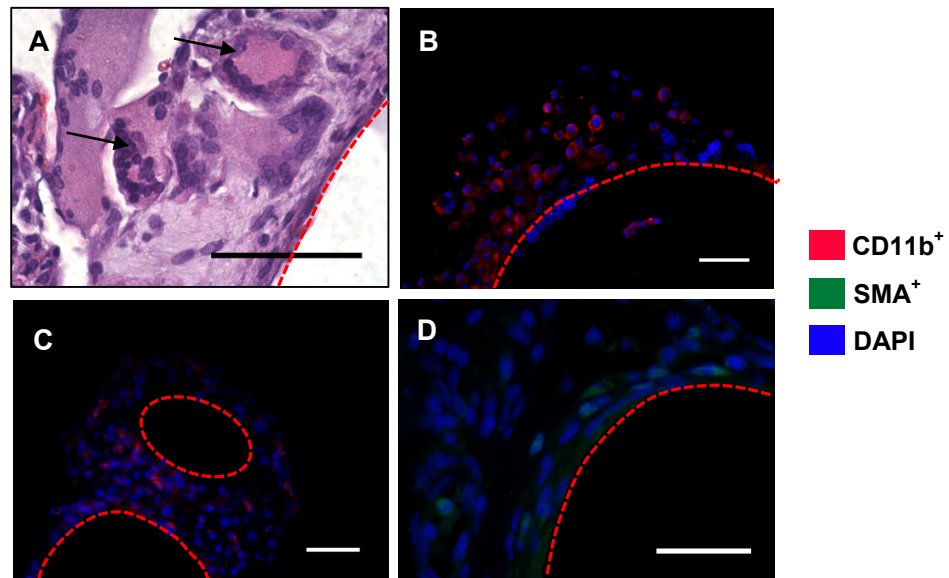
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**Supplementary Figure 1: Immune cell populations involved in the foreign body reaction to empty alginate spheres post general intraperitoneal (IP) implantation in non-human primates (NHP) (A-PLO-A, UPMVG-Ba<sup>2+</sup>, and UPMVG-Ca<sup>2+</sup>/Ba<sup>2+</sup> implemented in the clinical trials).**

**A)** H & E staining of day 7 retrieved spheres identify multinucleated foreign body giant cells (UPMVG-Ba<sup>2+</sup>). **B)** CD11b<sup>+</sup> staining (red) of day 7 retrieved spheres identify innate immune cells of myeloid origin (NKs, dendritic, macrophages, granulocytes, neutrophils) (A-PLO-A). **C)** CD11b<sup>+</sup> staining (red) of day 7 retrieved spheres (UPMVG-Ca<sup>2+</sup>/Ba<sup>2+</sup>). **D)** Post 1 month retrieval, empty spheres were embedded in fibrotic tissue and smooth muscle actin (SMA<sup>+</sup>) positive myofibroblasts (green) were found at the sphere/tissue interface (A-PLO-A). Scale bars = 50 μm. (Representative of 5-10 images acquired from each stain and sphere formulation).

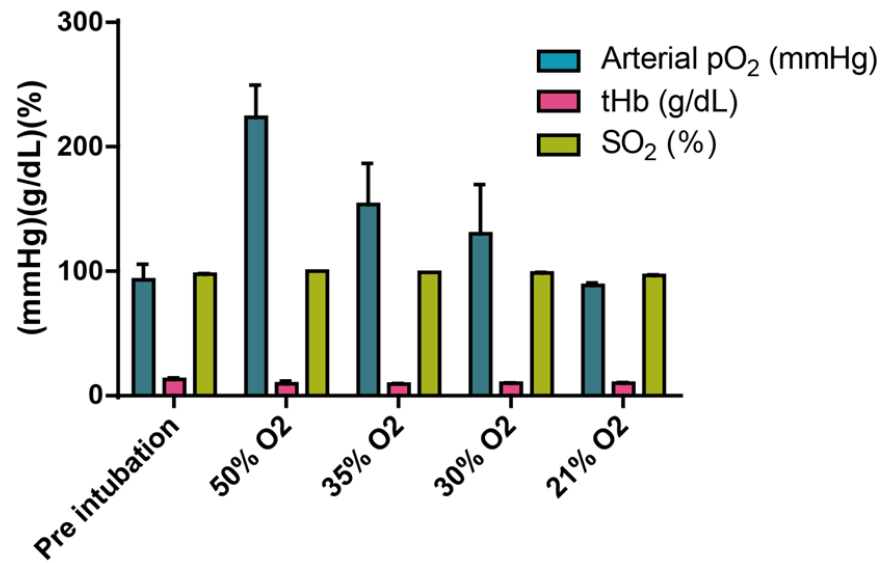
\*red dashes = sphere/tissue interface

\*black arrows = foreign body giant cells

**Supplementary Table 1:** Pericapsular fibrotic overgrowth (PFO) assessment of empty alginate sphere formulations post general IP implantation in NHP: percentage of sphere surface area covered by cellular overgrowth after 1 month.

Encapsulation Formulation	NHP (#)	Sphere Diameter (mm)	Average PFO surface area coverage of retrieved alginate spheres (% of spheres assessed per category per NHP)				Total spheres assessed (#)
			0-25%	25-50%	50-75%	75-100%	
A-PLO-A	PA7476	0.5	-	-	-	NR	NR
	PA7477	0.5	-	-	-	NR	NR
UPMVG-Ba <sup>2+</sup>	PA7480	0.5	-	-	-	NR	NR
UPMVG-Ca <sup>2+</sup> /Ba <sup>2+</sup>	PA7471	0.5	-	-	-	NR	NR
	PA7478	0.5	-	-	-	NR	NR
	CN7244	0.5	-	-	-	NR	NR
SLG20-Ba <sup>2+</sup>	CN8574	1.5	26.3	17.9	18.9	36.8	95
Z1-Y19-Ba <sup>2+</sup>	CN8564	1.5	69.9	17.5	2.7	9.8	143
	CN8565	1.5	56.6	15.7	19.7	7.9	76
	CN8558	1.5	10.3	8.8	14.7	66.2	68
Z2-Y12-Ba <sup>2+</sup>	CN8630	1.5	62.1	19.5	9.8	8.6	174
	CN8631	1.5	86.8	11.6	0.8	0.8	129
	CN8570	1.5	72.0	16.8	4.8	6.4	125
Z1-Y15-Ba <sup>2+</sup>	CN8564	1.5	76.2	17.9	2.4	3.6	84
	CN8565	1.5	70.0	20.0	5.0	5.0	120
	CN8558	1.5	67.2	18.8	4.7	9.4	64

\*NR = not retrievable due to fibrosis; assessed as 75-100% PFO



**Supplementary Figure 2: Arterial pO<sub>2</sub> of NHP intubated with different FiO<sub>2</sub> (fraction of inspired oxygen). FiO<sub>2</sub> of 21% O<sub>2</sub> during surgical intubation matches an NHP breathing normal room air and was used for intubation during pO<sub>2</sub> measurements of transplantation sites in NHP. Arterial pO<sub>2</sub> (mmHg), total hemoglobin concentration (tHb) (g/dL) and saturation of oxygen (SO<sub>2</sub>) (%) of NHP (*n* = 2) were determined from blood draws from an arterial line and the IDEXX VetStat Electrolyte and Blood Gas Analyzer under different percentages of FiO<sub>2</sub> (mean ± SD).**

**Supplementary Table 2: Partial oxygen pressures (pO<sub>2</sub>) of transplantation sites for encapsulated islets in NHP (*n* = 3 measurements per location; *n* = 3 NHP; mean ± SD)**

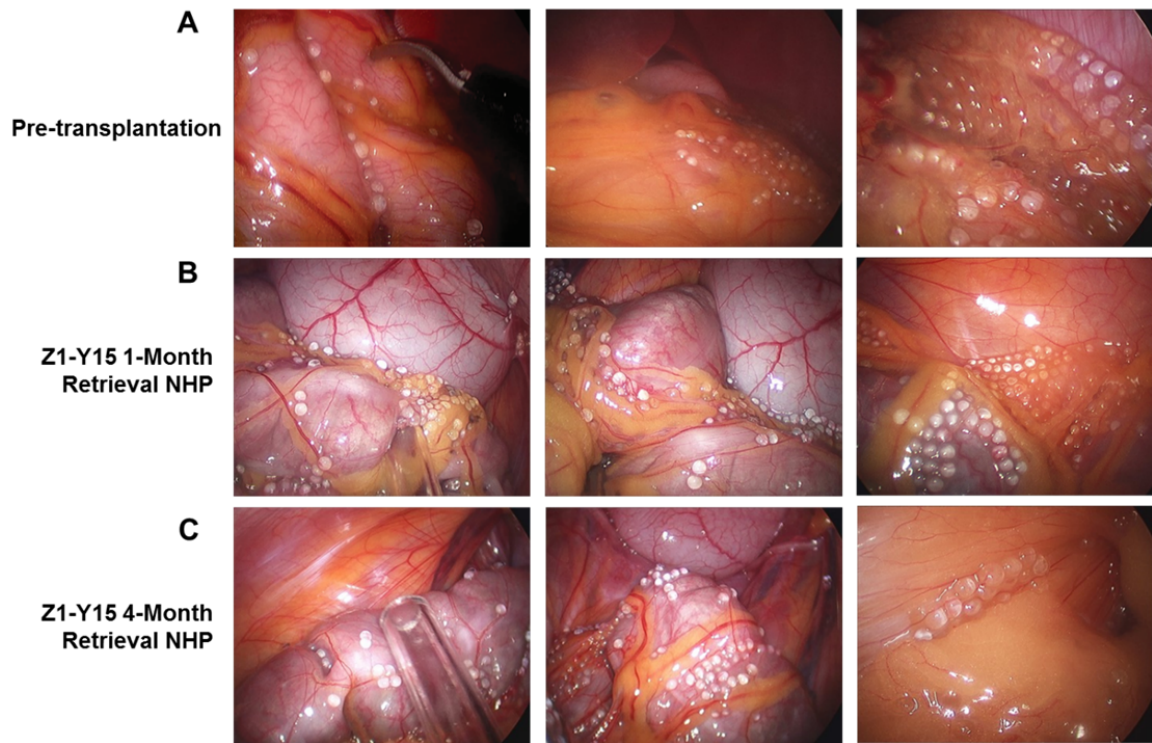
Anatomical Location	PO <sub>2</sub> (%)	PO <sub>2</sub> (mmHg)	Hb O <sub>2</sub> Saturation (%)
<b>Intramuscular</b>	4.2 ± 0.6	31.8 ± 4.4	95.2 ± 0.7
<b>Kidney capsule</b>	6.5 ± 0.5	48.7 ± 3.9	95.7 ± 1.0
<b>Liver</b>	5.6 ± 0.7	42.1 ± 7.2	96.3 ± 1.8
<b>Pancreas</b>	5.3 ± 1.4	39.6 ± 9.5	95.1 ± 1.8
<b>General Intra-peritoneal space (IP)</b>	4.1 ± 0.9	30.7 ± 6.8	93.8 ± 2.4
<b>Subcutaneous</b>	5.1 ± 0.8	39.0 ± 6.3	95.6 ± 0.7
<b>Bursa omentalis</b>	4.6 ± 1.4	35.1 ± 11.0	93.2 ± 2.4

**Supplementary Table 3:** Fisher's LSD statistical analysis of partial oxygen pressures (pO<sub>2</sub>) of transplantation sites for encapsulated islets in NHP

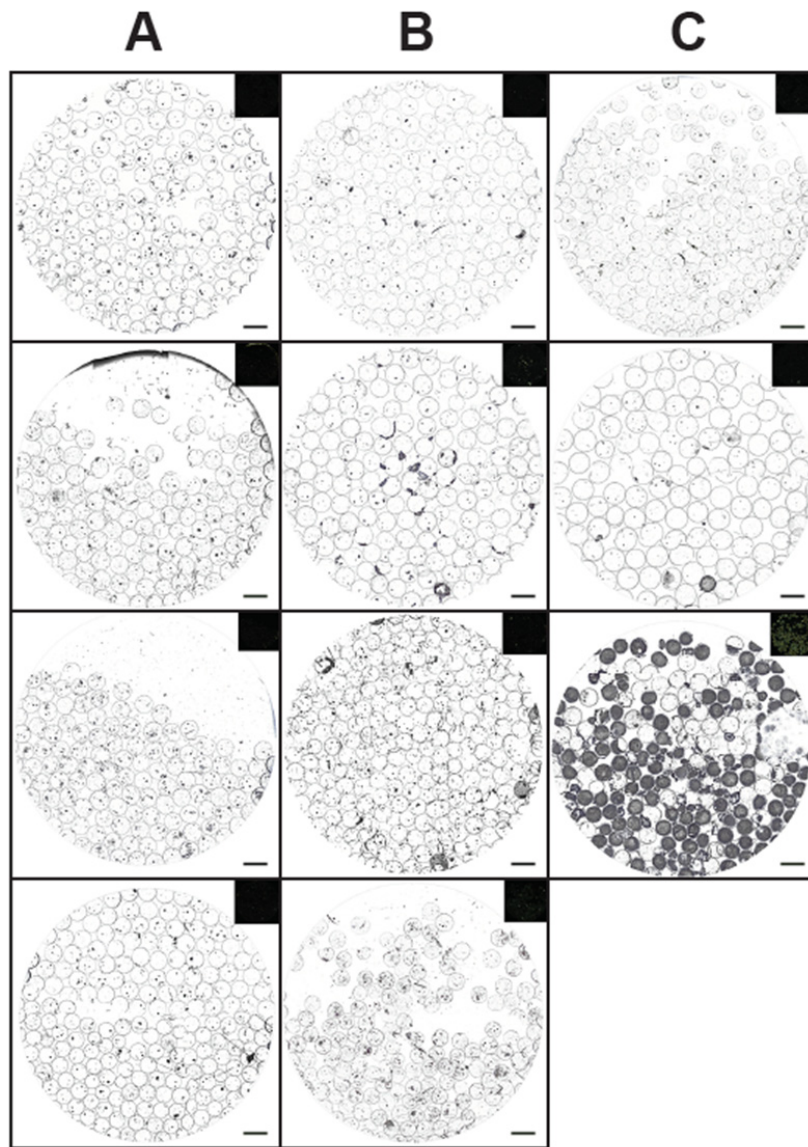
<b>Anatomical Location uncorrected Fisher's LSD</b>	<b>Mean Diff.</b>	<b>Significant?</b>	<b>Summary</b>	<b>Individual P Value</b>
<b>Kidney vs. General IP Space</b>	17.94	Yes	****	<b>&lt; 0.0001</b>
<b>Kidney vs. Intramuscular</b>	16.83	Yes	****	<b>&lt; 0.0001</b>
<b>Kidney vs. Bursa Omentalis</b>	13.58	Yes	***	<b>0.0001</b>
<b>Kidney vs. Subcutaneous</b>	9.667	Yes	**	<b>0.0083</b>
<b>Kidney vs. Pancreas</b>	9.111	Yes	*	<b>0.0126</b>
<b>Kidney vs. Liver</b>	6.556	No	ns	<b>0.0696</b>
<b>Pancreas vs. General IP Space</b>	8.833	Yes	**	<b>0.0055</b>
<b>Pancreas vs. Intramuscular</b>	7.722	Yes	*	<b>0.0334</b>
<b>Pancreas vs. Bursa Omentalis</b>	4.472	No	ns	<b>0.1833</b>
<b>Pancreas vs. Subcutaneous</b>	0.5556	No	ns	<b>0.8763</b>
<b>Pancreas vs. Liver</b>	-2.556	No	ns	<b>0.4748</b>
<b>Bursa Omentalis vs Liver</b>	-7.028	Yes	*	<b>0.0383</b>
<b>Bursa Omentalis vs. Subcutaneous</b>	-3.917	No	ns	<b>0.2431</b>
<b>Bursa Omentalis vs. Intramuscular</b>	3.25	No	ns	<b>0.332</b>
<b>Bursa Omentalis vs. General IP Space</b>	4.361	No	ns	<b>0.1255</b>
<b>General IP Space vs. Liver</b>	-11.39	Yes	***	<b>0.0004</b>
<b>General IP Space vs. Subcutaneous</b>	-8.278	Yes	**	<b>0.009</b>
<b>General IP Space vs. Intramuscular</b>	-1.111	No	ns	<b>0.7194</b>
<b>Subcutaneous vs. Liver</b>	-3.111	No	ns	<b>0.3847</b>
<b>Subcutaneous vs. Intramuscular</b>	7.167	Yes	*	<b>0.0478</b>
<b>Liver vs. Intramuscular</b>	10.28	Yes	**	<b>0.0052</b>

**Supplementary Table 4:** Transplantation characteristics of encapsulated allogeneic islets transplanted into the bursa omentalis of NHP (1,000 islets/1 mL alginate solution)

<b>Encapsulation Formulation</b>	<b>NHP#</b>	<b>Dose Transplanted (volume spheres/kg NHP)</b>	<b>Dose Transplanted (# islets/kg NHP)</b>	<b>NHP sex (recipient)</b>	<b>NHP sex (donor)</b>
<b>SLG20-Allo Retrieved at 1 Month</b>	CN8632	1.8 mL/kg	2,650 islets/kg	female	female
	CN8700	2.3 mL/kg	2,300 islets/kg	male	male
<b>Z1-Y15-Allo Retrieved at 1 Month</b>	CN8708	1.9 mL/kg	1,950 islets/kg	male	male
	CN8798	0.9 mL/kg	950 islets/kg	male	male
	CN8802	1.0 mL/kg	1,000 islets/kg	male	female
<b>Z1-Y15-Allo Retrieved at 4 Months</b>	CN8799	1.1 mL/kg	1,050 islets/kg	male	male
	CN8800	1.2 mL/kg	1,200 islets/kg	male	female
	CN8801	1.2 mL/kg	1,150 islets/kg	male	female

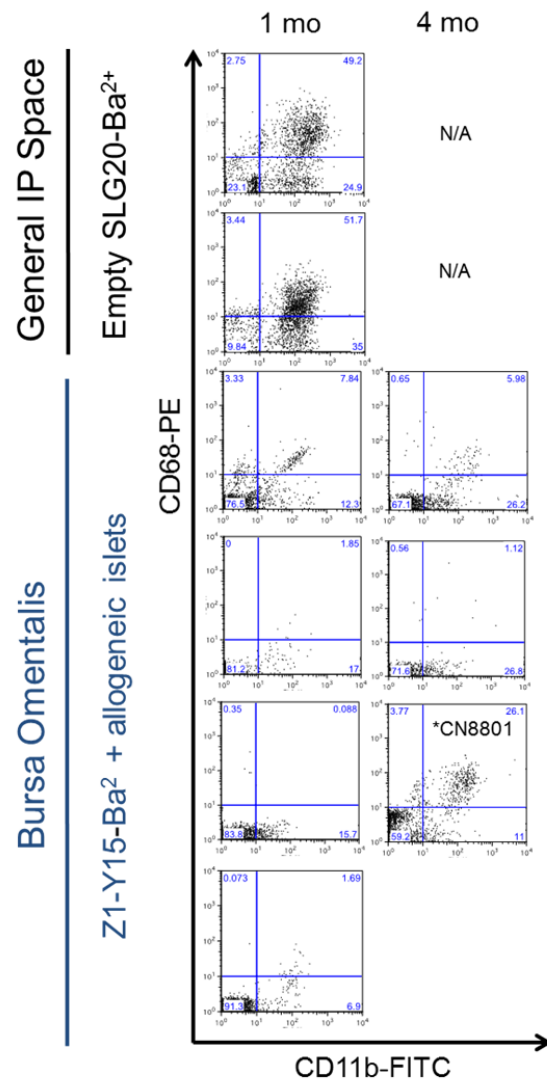


**Supplementary Figure 3: 1.5 mm Z1-Y15 spheres with encapsulated cynomolgus islets transplanted into the bursa omentalis of NHP remain well distributed with no gross clumping in the Douglas space after 1 month and 4 months post transplantation. A)** Laparoscopic images showing translucent spheres with allogeneic islets immediately post-infusion (Representative of 3-10 images acquired per  $n = 7$  NHP transplants). **B)** Representative laparoscopic images show well distributed translucent spheres during the 1-month retrieval ( $n = 4$  NHP) (Representative of 10-16 images acquired per 4 NHP), **C)** and during the 4-month retrieval ( $n = 3$  NHP) (Representative of 10-15 images acquired per 2/3 NHP). Retrieved Z1-Y15 spheres with encapsulated islets from omental resections are portrayed in Figure 3 and Supplementary Figure 4.

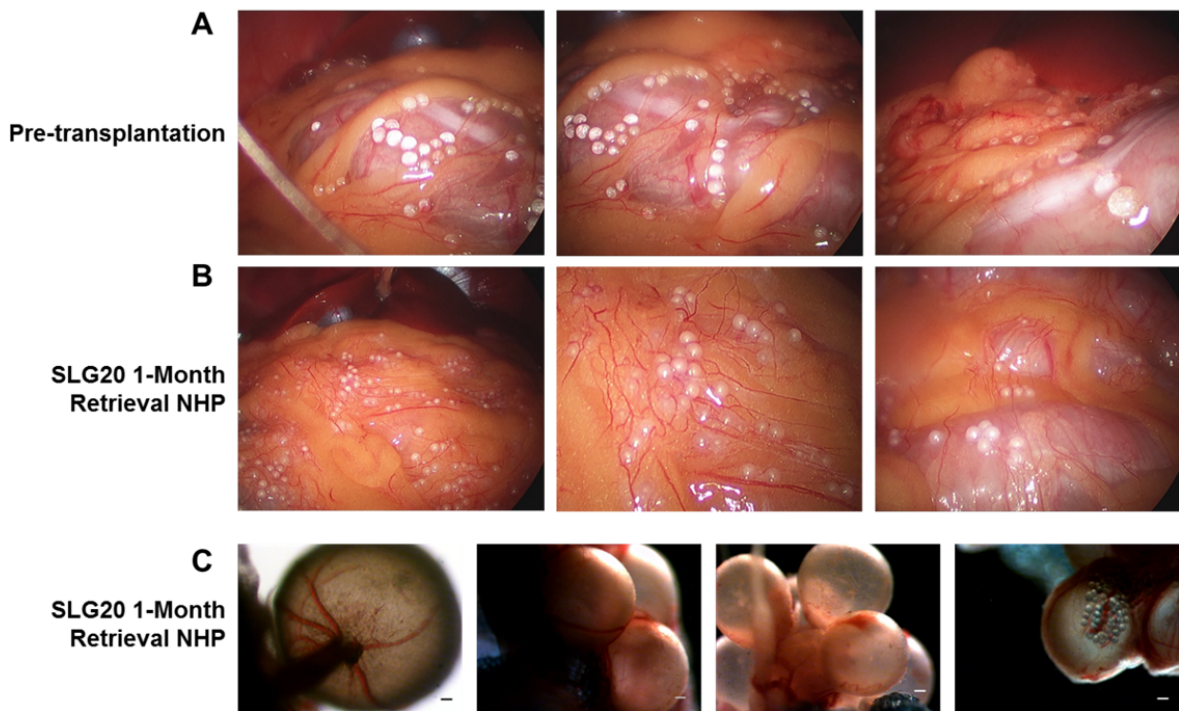


**Supplementary Figure 4: 1.5 mm Z1-Y15 spheres with encapsulated cynomolgus islets transplanted into the bursa omentalis of NHP are free of fibrosis in 6/7 primates post transplantation.** Individual inverted phase contrast of Z1-Y15 spheres with encapsulated allogeneic islets: **A)** pre-transplantation (pretx); **B)** post retrieval from each NHP at 1 month ( $n = 4$  NHP); **C)** post retrieval from each NHP 4 months ( $n = 3$  NHP). Scale bars = 2 mm.





**Supplementary Figure 5: Flow cytometry contour plots and gating strategy used for CD68-PE/CD11b-FITC stained cells dissociated from the surface of retrieved spheres. (Empty SLG20-Ba<sup>2+</sup>  $n = 2$  NHP at 1 month; Z1-Y15-Ba<sup>2+</sup> spheres with allogeneic islets  $n = 4$  NHP at 1 month, and  $n = 3$  at 4 months).**

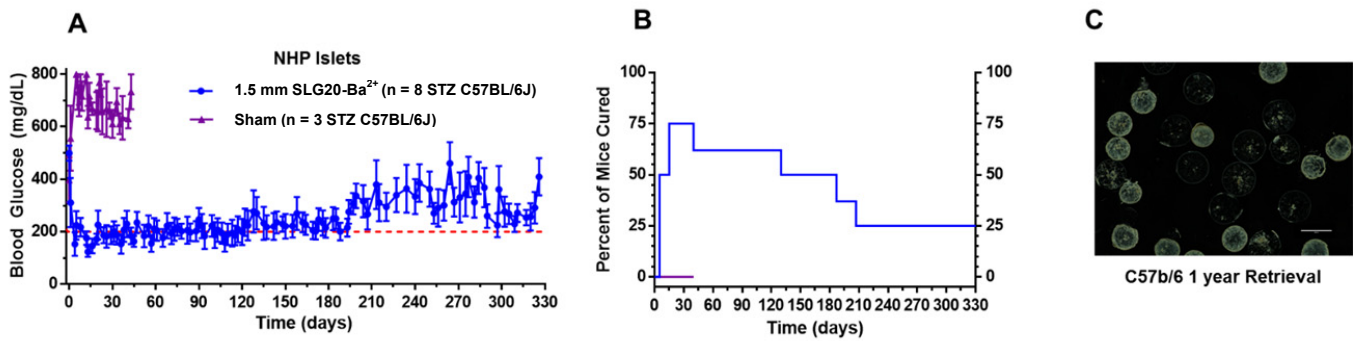


**Supplementary Figure 6: 1.5 mm SLG20 spheres with encapsulated cynomolgus islets transplanted into the bursa omentalis of NHP elicits a foreign body response 1 month post-transplantation.** **A)** Laparoscopic images of translucent spheres pre-transplantation (Representative of 9 images acquired). **B)** Laparoscopic images of the 1 month retrieval show the SLG20 encapsulated islets were well distributed within the bursa site but opaque due to pericapsular fibrotic overgrowth ( $n = 1$  NHP) (Representative of 17 images acquired). **C)** Bright-field and dark-field images of excised spheres that were adhered to omental tissue at 1-month (scale bars = 200  $\mu\text{m}$ ) (Representative of 10 images acquired).

**Supplementary Table 5:** Pericapsular fibrotic overgrowth (PFO) assessment of spheres with encapsulated allogeneic islets post bursa omentalis transplantation in NHP: percentage of sphere surface area covered by cellular overgrowth at 1-month and 4-months retrievals.

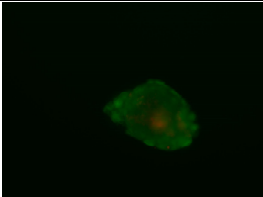
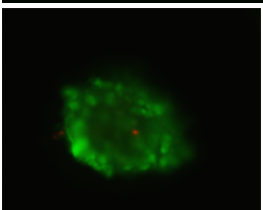
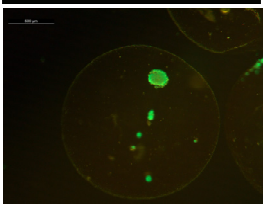
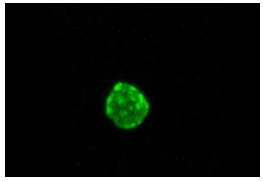
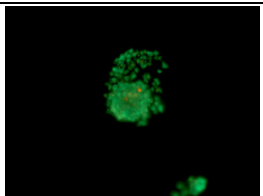
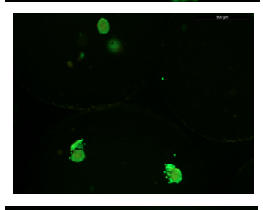
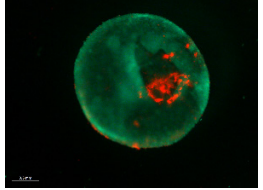
Encapsulation Formulation	NHP#	Sphere Diameter (mm)	Average PFO surface area coverage of retrieved spheres (% of spheres assessed per category per NHP)				Total spheres assessed (#)
			0-25%	25-50%	50-75%	75-100%	
<b>SLG20-Allo Retrieved 1 Month</b>	CN8632	1.5	-	-	-	NR	NR
<b>Z1-Y15-Allo Retrieved 1 Month</b>	CN8700	1.5	98.3	0.8	0	0.8	121
	CN8708	1.5	97.5	1.9	0	0.6	90
	CN8798	1.5	98.7	1.3	0	0	152
	CN8802	1.5	96	4	0	0	125
<b>Z1-Y15-Allo Retrieved 4 months</b>	CN8799	1.5	95.5	3.3	0	1.1	160
	CN8800	1.5	29.3	2.4	1.2	67.1	167
	CN8801	1.5	92.2	7.8	0	0	128

\*NR = not retrievable due to fibrosis; assessed as 75-100% PFO



**Supplementary Figure 7: 1.5 mm SLG20 spheres with encapsulated cynomolgus islets promotes long-term glycemic control in immune-competent C57BL/6J mice, but resulted in fibrosis in NHP post 1 month.** **A)** Average daily blood glucose levels of STZ induced diabetic C57BL/6J mice transplanted with a marginal islet mass of 1,500 cynomolgus islets in the IP space (1.5 mm SLG20  $n = 8$  mice total over  $n = 2$  batches of cyno isolations/encapsulations; sham STZ C57BL/6J  $n = 3$ ; mean  $\pm$  SEM). **B)** Kaplan-Meier curve plot of STZ C57BL/6J mice. **C)** Dark field image of SLG20 encapsulated cynomolgus islets retrieved at 1 year from the 2 C57BL/6J mouse with curative BG levels (representative of 7 images acquired).

**Supplementary Table 6:** Viability assessments of Z1-Y15 encapsulated allogenic islets for individual NHP retrievals at 1-month and 4-months.

Encapsulation Formulation	NHP#	Viability Assessment Post Retrieval (% Viable cells per islet; Upper:Lower 95% CI of Median)	Wilcoxon Signed Rank Test; compared to 75% viability; two tailed	Representative Fluorescent Images (5-10 images per NHP) (FDA/PI)
<b>Z1-Y15-Allo Retrieved 1 Month</b>	CN8700	97:93	$p < 0.0001$	   
	CN8708	95:89	$p < 0.0001$	
	CN8798	97:80	$p = 0.04$	
	CN8802	98:85	$p = 0.0001$	
<b>Z1-Y15-Allo Retrieved 4 months</b>	CN8799	93:80	$p = 0.04$	  
	CN8801	98:87	$p < 0.0001$	
	CN8800	No viable islets present	NA	

**Supplementary Video 1 Legend: Non-invasive laparoscopic transplantation technique for hydrogel spheres into the bursa omentalis.**

Following the insertion of three trocars, an endoscopic grasping forceps is used to gently lift the stomach, and a small incision is made into an avascular portion of the gastrocolic ligament. A 60 mL lavage syringe contains the hydrogel spheres dispersed in saline and is connected to a 2 mL serological pipette via silicone tubing. The pipette is inserted through the trocar and carefully into the opening into the lesser sac. The spheres are then gently infused into the bursa omentalis. The stomach is gently lowered to seal the opening and manipulation by the laparoscopic scissors shows that the spheres are dispersed within the omental bilayer forming the greater omentum.

**Supplementary Video 2 Legend: Non-invasive laparoscopic retrieval of Z1-Y15 spheres containing allogeneic islets performed 1-month post transplantation.**

Following insertion of the camera into the peritoneal cavity of NHP, Z1-Y15 spheres containing allogeneic islets were found uniformly distributed throughout the greater omentum bilayer (bursa omentalis) with substantially reduced clumping in the Douglas Space compared to general IP space transplantation. The spheres were translucent and could be easily manipulated which is indicative of non-fibrosed spheres that are not adhered to omental tissue. A saline flush was conducted on top of greater omentum. The aspirated saline contained no spheres verifying that post-transplantation the spheres remain within the bursa omentalis site. This was similarly verified at the 4 month retrievals.