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Correlation between *In Vivo* and *Ex Vivo* Markers of Functional Beta Cell Mass in Alginate-Encapsulated Human Beta Cell Implants in Preclinical Model

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AIM AND EXPERIMENTAL DESIGN

Our center develops methods to measure the functional beta cell mass in grafts before implantation (*in vitro*) and in retrieved implants (*ex vivo*), and assesses their relationship with metabolic outcome (*in vivo*). The present study investigates the functional capacity of alginate-encapsulated human beta cell preparations. The cells were injected at a defined dose (40x10⁶ beta cells/kg BW) in the peritoneal cavity (IP) or in the subcutis (SC) of normal NOD/*scid* mice. The animals were followed for 20 weeks through plasma hu-C-peptide levels following glucose stimulation and glycemia at basal and after glucose loading. At post-transplant (PT) week 20, implants were retrieved, the capsules were sampled to determine beta cell number and secretory capacity. Both parameters of functional beta cells were compared with the initial values in the graft.

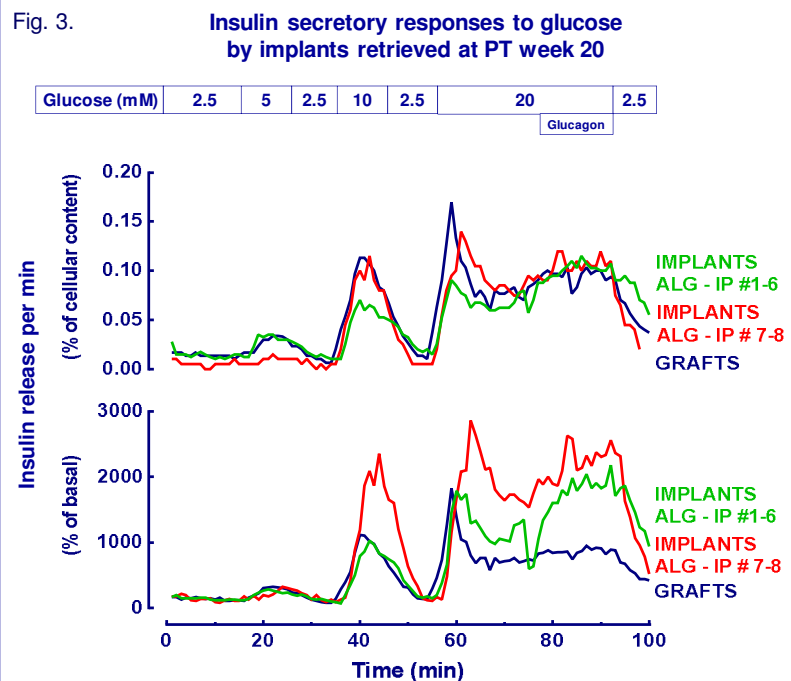
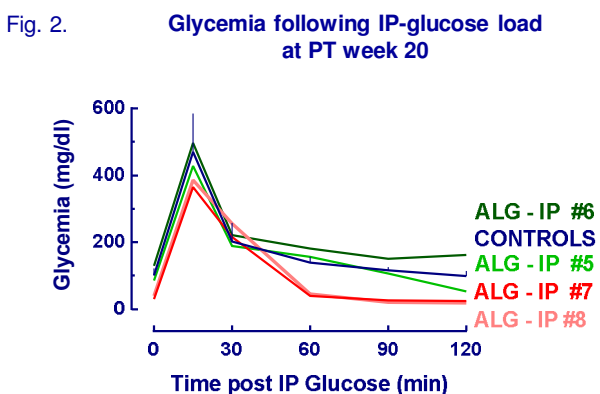
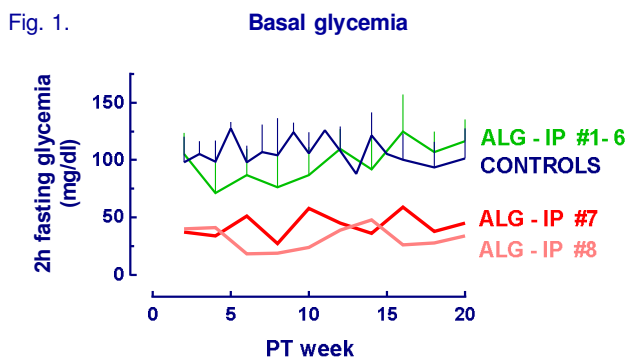
RESULTS

Table 1. Number of recipients with hu-C-peptide > 0.5 ng/ml at PT week

Implant	2	10	20
ALG - IP	13/13	9/9	8/8
ALG - SC	9/9	2/6	2/6

Table 2. Correlation between plasma hu-C-peptide levels and beta cell number in implants at PT week 20

Implant	hu-C-peptide (ng/ml)	Beta cell number (% of number in graft)	
ALG - IP	#1	1.32	15.2
	#2	0.68	11.9
	#3	0.63	-
	#4	1.99	19.1
	#5	1.17	46.5
	#6	1.30	-
	#7	4.26	73.6
	#8	4.56	92.4
ALG - SC	#1	1.23	41.2
	#2	1.56	48.5



CONCLUSIONS

Alginate-encapsulated human beta cell preparations can establish, for at least 20 weeks, a functional beta cell mass, as reflected by plasma hu-C-peptide levels > 0.5 ng/ml following a glucose stimulus. This is the case for all IP implants, but only a few SC (Table 1). At PT week 20, the majority of the functional implants (6/8 IP and 2/2 SC) showed levels in the range 0.5-2 ng/ml, whereas 2 IP implants achieved levels higher than 3 ng/ml, the level needed to correct hyperglycemia. These two animals showed a lower glycemia at basal (Fig. 1) and from 60 min after an IP glucose load (Fig. 2). They exhibited a higher functional beta cell mass *ex vivo* both in beta cell number and activity (Table 2, Fig. 3).

This case study indicates a correlation between *in vivo* metabolic parameters and *ex vivo* measurements of the functional beta cell mass in human beta cell implants. The results demonstrate that human IP implants in mice can reduce basal glycemia and achieve circulating hu-C-peptide levels as in normal man.