

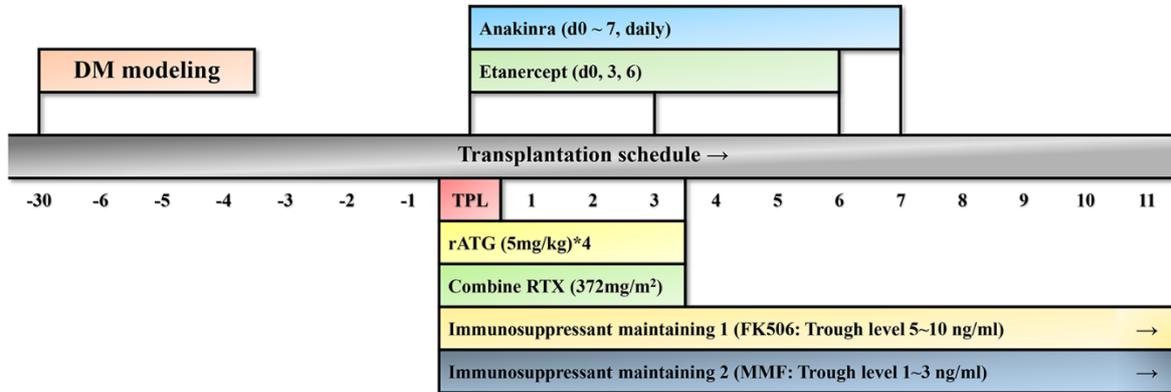
Supplementary information

Marginal transplantation dose study for the treatment of insulin-independent type 1 diabetes after allogeneic islet transplantation in *Macaca fascicularis* monkeys

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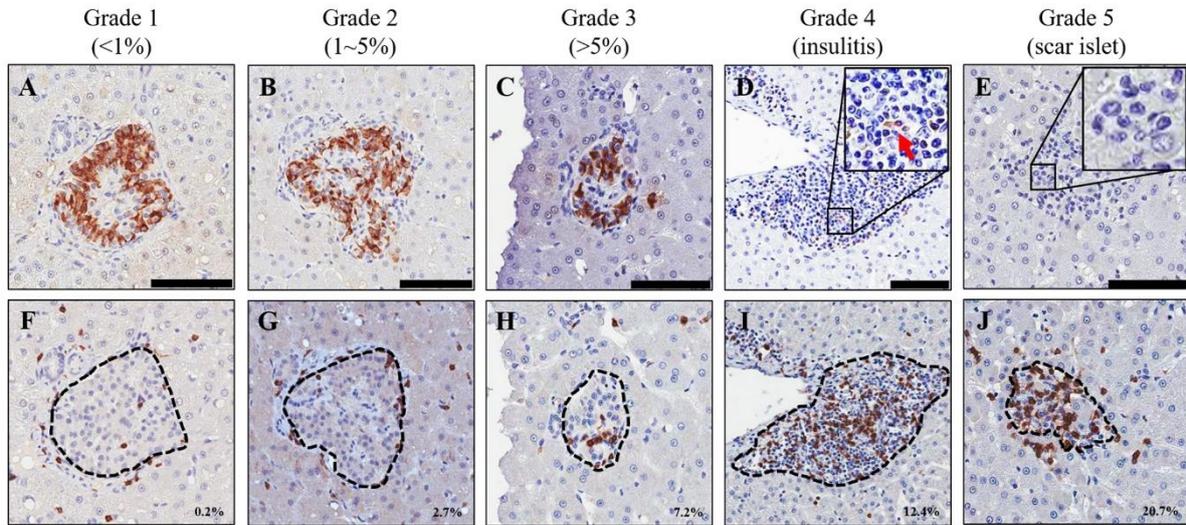
Supplemental figure 1.

Immunosuppressant regime scheme



Supplemental Figure S1. The schedule for the immunosuppressant regime. Type 1 diabetes was induced by pancreatectomy and streptozotocin (STZ) administration at least 30 days before transplantation. On transplantation day, the monkeys received rabbit anti-thymocyte globulin (ATG) four times at 12-hour intervals to a cumulative dose of 20 mg/kg as induction immunosuppression. Rituximab (RTX) injections at a dose of 375 mg/m² were added as combination induction immunosuppression in monkeys E, F and G. All monkeys received oral tacrolimus (FK506) and mycophenolate mofetil (MMF) as maintenance immunosuppressive drugs. To prevent inflammatory events, etanercept was given on the day of transplantation (day 0) and on days 3 and 6. Subcutaneous injections of anakinra were also given daily from days 0 to 7.

Supplemental figure 2.



Supplemental Figure S2. Grading criteria for T cell-infiltrated islets. After immunohistochemistry staining, the detected islets were analyzed using the Aperio Positive Pixel Count algorithm (version 9.1). CD3⁺ T cell infiltration rate was graded according to the amount of infiltration within the islet area and morphology. **(a)**, **(f)** Grade 1 was determined as a CD3⁺ T cell expression rate of less than <1%. **(b)**, **(g)** Grade 2 was determined as a CD3⁺ T cell expression rate between 1 and 5%. **(c)**, **(h)** Grade 3 was determined as a CD3⁺ T cell expression rate of more than >5%. **(d)** and **(i)** Grade 4, in which the islets rarely express insulin (red arrowed, <1%) because of near-destruction caused by a massive infiltration of T cells, is called *insulinitis*. **(e)** and **(j)** Grade 5, in which the islets do not express insulin because of destruction by a massive infiltration of T cells, is called *scar islet*. Black dotted lines indicate islet boundaries. Brown indicates the target protein in each result (A–E = insulin, F–J = CD3). The CD3⁺ T cell expression rate is marked in the lower right of the second panel (scale bars = 100 μ m).

Supplemental table 1.

Month	Group	Value	Diameter		Beta cell expression rate		Alpha cell expression rate		CD3 ⁺ T cell expression rate		CD20 ⁺ B cell expression rate		IAPP expression rate	
			(µm)		(%)		(%)		(%)		(%)		(%)	
			IDS [†]	CDS ^{††}	IDS	CDS	IDS	CDS	IDS	CDS	IDS	CDS	IDS	CDS
1M	G2	<i>n</i>	11	4	11	4	7	4	7	4	7	4	4	4
		Ave	102.46	126.49	77.34	71.13	29.60	31.39	1.60	1.66	0.43	0.00	1.59	1.59
		SEM	11.85	19.73	5.36	8.82	5.11	8.78	0.54	0.47	0.43	0.00	1.08	1.08
	P value	ns (0.1570)		ns (0.2795)		ns (0.4268)		ns (0.4764)		na ^{†††}		ns (0.5000)		
	G3	<i>n</i>	15	5	15	5	10	5	10	5	11	5	8	5
		Ave	80.38	105.90	78.31	80.20	25.59	23.61	0.26	0.46	0.00	0.00	0.16	0.17
SEM		7.26	15.56	5.10	2.61	5.47	6.21	0.19	0.37	0.00	0.00	0.08	0.10	
P value	ns (0.5690)		ns (0.4180)		ns (0.4149)		ns (0.2875)		na		ns (0.4856)			
2M	G2	<i>n</i>	59	28	59	28	48	28	47	28	40	28	39	28
		Ave	108.40	143.20	74.48	67.66	26.17	21.46	1.58	1.02	0.03	0.04	0.34	0.21
		SEM	7.03	10.53	1.85	2.58	2.52	2.69	0.38	0.28	0.03	0.04	0.11	0.09
	P value	** (0.0033)		* (0.0173)		ns (0.1151)		ns (0.1526)		ns (0.4250)		ns (0.2003)		
	G3	<i>n</i>	39	26	39	26	33	26	33	26	33	26	28	26
		Ave	83.00	93.40	78.29	79.01	12.15	13.15	0.88	0.81	0.03	0.01	0.23	0.24
SEM		6.77	9.31	1.81	2.15	2.24	2.63	0.18	0.20	0.02	0.00	0.07	0.07	
P value	ns (0.1795)		ns (0.4010)		ns (0.3854)		ns (0.2976)		ns (0.2004)		ns (0.4453)			

†IDS (incomplete data set), ††CDS (complete data set), †††na (not available, did not analyze due to inadequate data)

Supplemental Table S1. Results of the statistical analyses and numbers of islets found in liver biopsies