Mouse Models for Studying Human Islet Transplantation

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Can a mouse model form an in vivo ‘potency’ assay?

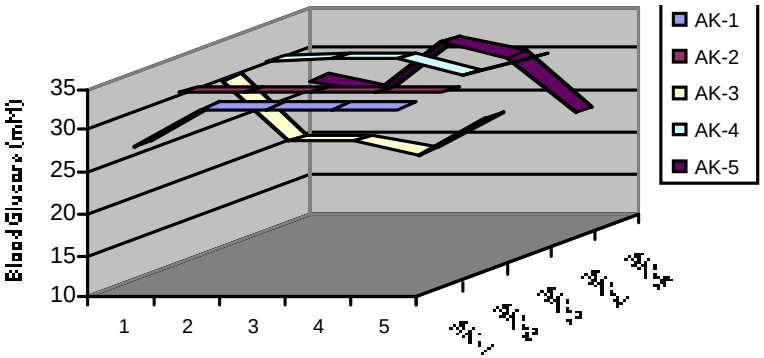
Mouse Models for Assessing Human Islet Function

- Immune-suppressed wild-type mice (e.g. anti-CD4)
- T cell-deficient nude (nu/nu) mice
- Severe-combined immune-deficient (*SCID*)
- Recombinase activating gene 1,2-deficient (*Rag*$^{-/-}$)

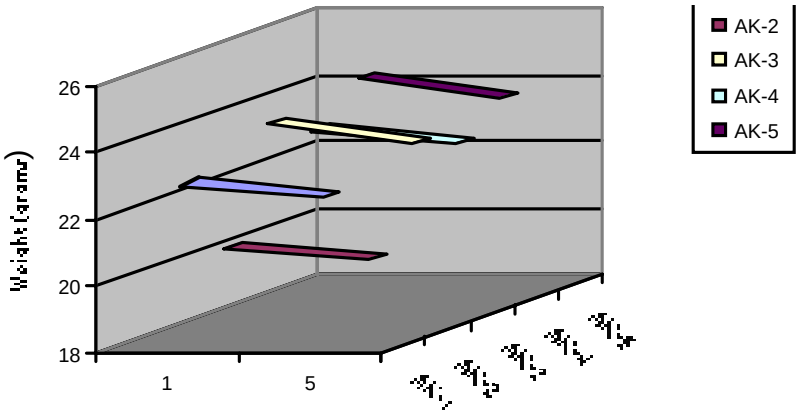
Insulin *akita* Mutation

- Missense mutation (Cys96Tyr) in Insulin 2 (Ins 2) gene
- Prevents appropriate folding of pro-insulin
- Autosomal-dominant (chromosome 7)
- Functions as a ‘dominant-negative’
- Durable and irreversible hyperglycemia (>450-500mg/dl)
- Males more severe than females

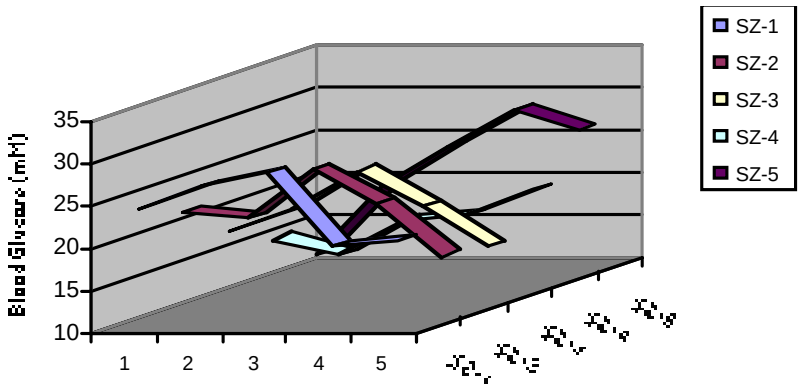
Rag1$^{-/-}$ *akita* Blood Glucose



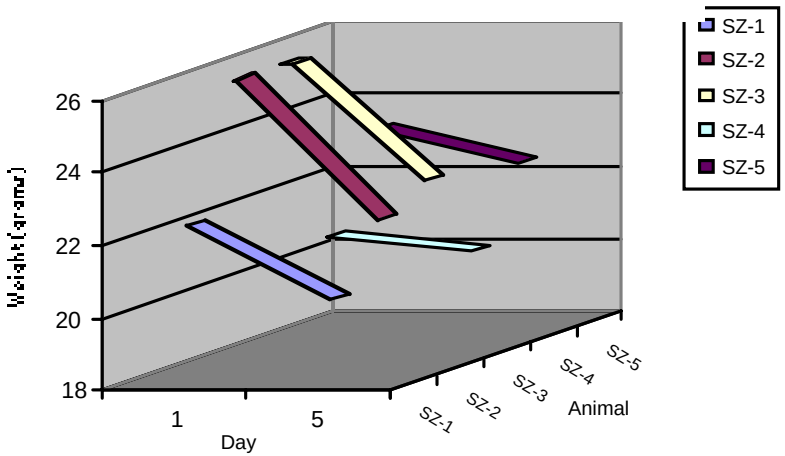
Rag1$^{-/-}$ *akita* Weight Change



SZ Blood Glucose



SZ Weight Change



Utility of *akita* mice as islet transplant recipients

Mathews, CE *et al.* *Transplantation.* 73:1333, 2002

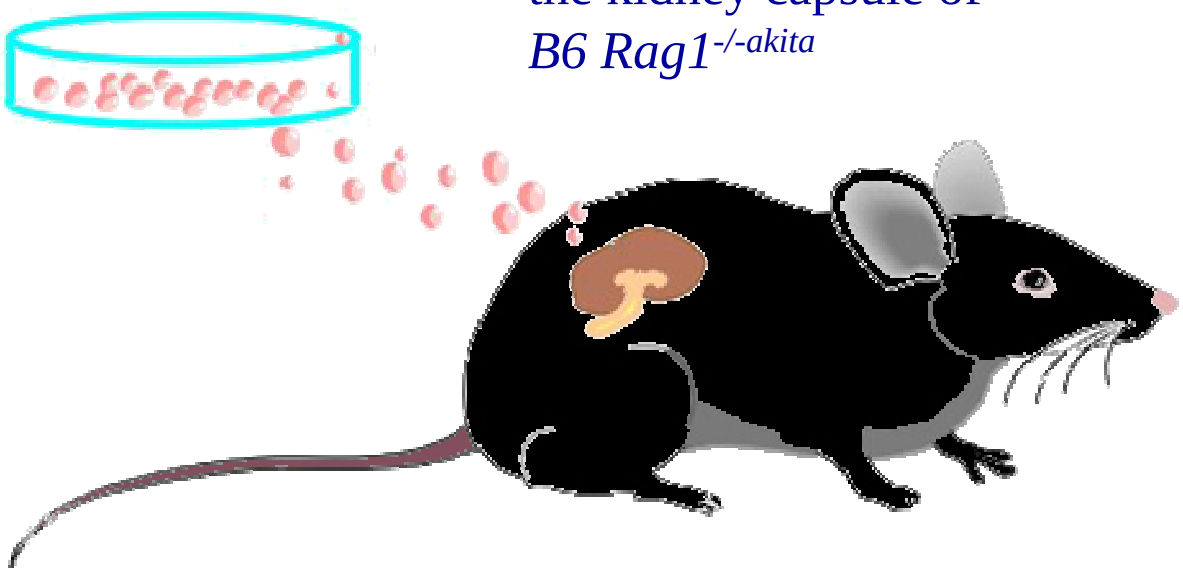
Islet Function in C57Bl/6^{akita} Mice

Donor	n	Graft Function (Days)
ISOGRAFTS (C57Bl/6)	8	> 100 (x8)
ALLOGRATS (BALB/c)	3	9, 9, 12

Islet Transplantation in B6 Rag1$^{-/-akita}$ Mice

Donor Islets

Transplant 2000 IEQ under the kidney capsule of *B6 Rag1$^{-/-akita}$*



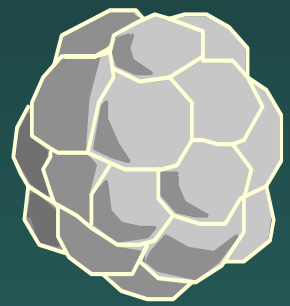
- Monitor blood glucose
- Nephrectomy – immunohistochemistry

Correlation between in vitro assays and in vivo function in *Rag1*$^{-/-akita}$ mice

Purity	Viability	S.I.	In vivo function (>30 days)
60	60	1.6	Yes
90	80	3.0	Yes
80	75	5.2	Yes
85	72	2.4	Yes
90	70	2.4	Yes
40	60	0.8	*No*
60	77	0.2	*No*
60	60	0.6	*No*
60	60	2.1	*No*
75	75	4.0	*No*
50	60	1.1	Yes

Immune Injury

Non-Immune Injury



Islets

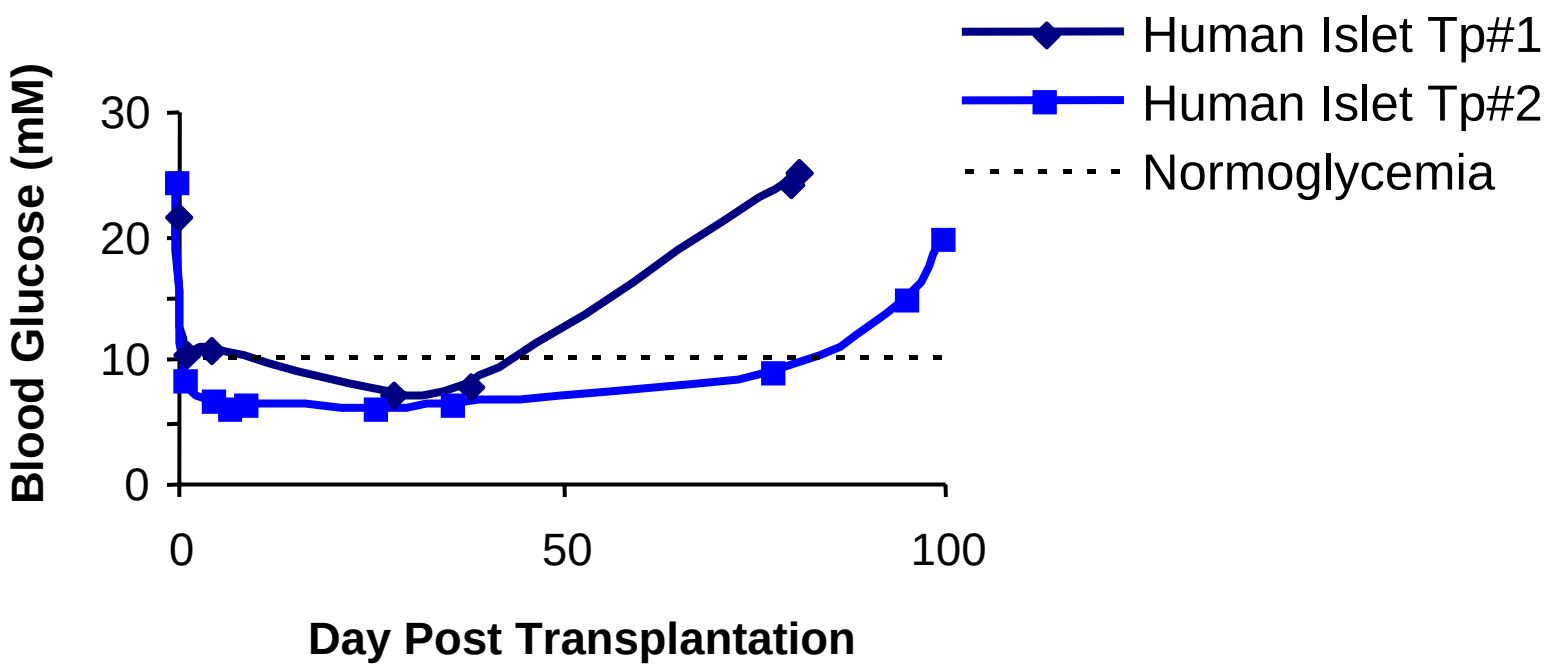
Isolated Islets Highly Express Proteins Associated with ER-Distress

Nicolls, MR *et al.* *J. Proteome. Res.* 2:199, 2003

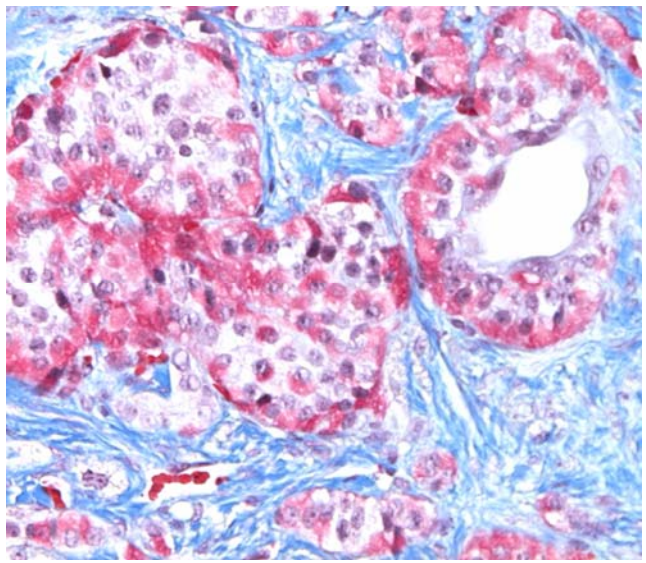
Function of Islet Grafts in *Rag1-/-* Recipients

Donor	n	Graft Function (days)
Mouse	8	>100 (x 8)
Rat (WF)	9	>100 (x 9)
Porcine	12	>100 (x 12)
Human	17	47,65,74,91,94 >100 (x12)

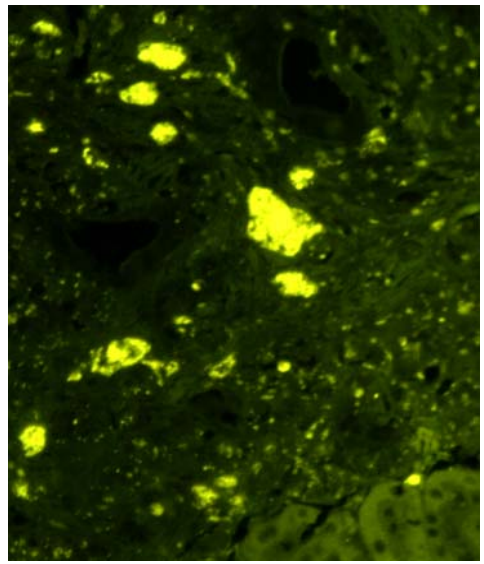
Spontaneous Failure of Human Islets *Rag1*$^{-/-}$*akita* Mice



Pathology of Failed Human Islets (day 70)

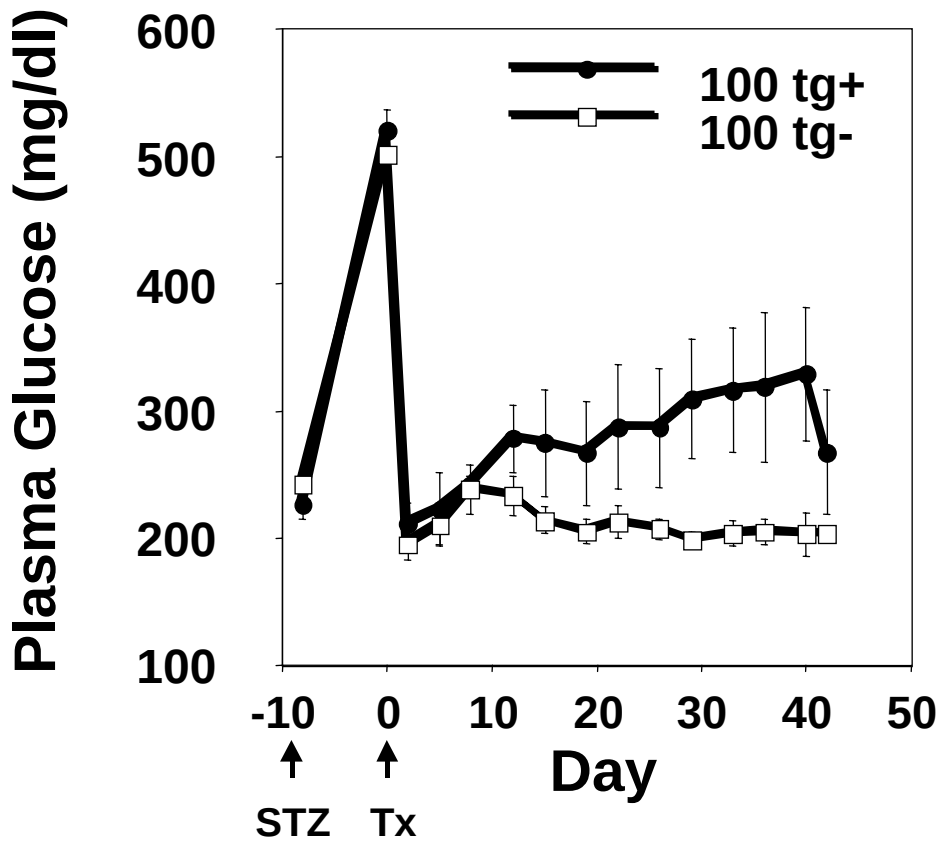


Fibrosis
(Tri-Chrome)



Amyloid
(Thyoflavin S)

Failure of hIAPP Transgenic Mouse Islets



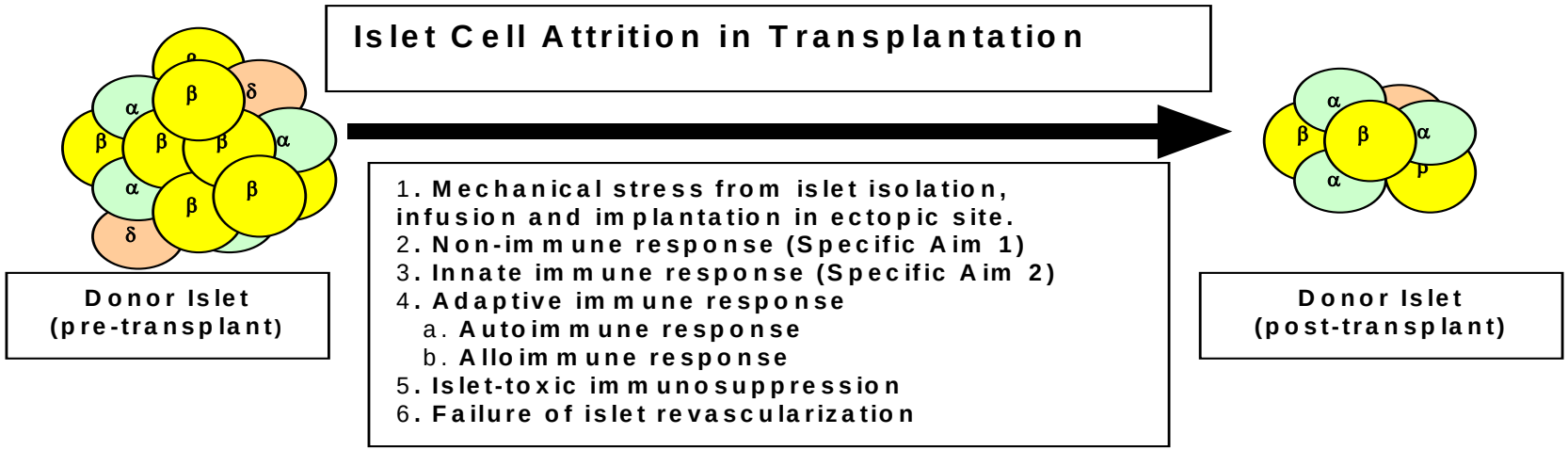


Figure 1. Factors influencing loss of islet cells following transplantation.

Summary / Conclusions

- Spontaneously diabetic *akita* mice demonstrate a stable and irreversible model of hyperglycemia
- Diabetic *akita* mice can be readily maintained for 2-3 months prior to transplantation
- Human islets can reverse diabetes in immune-deficient *akita* mice (*Rag1*$^{-/-akita}$)
- Human islets can spontaneously fail over time from non-immune factors (metabolic distress?)

Collaborators

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