

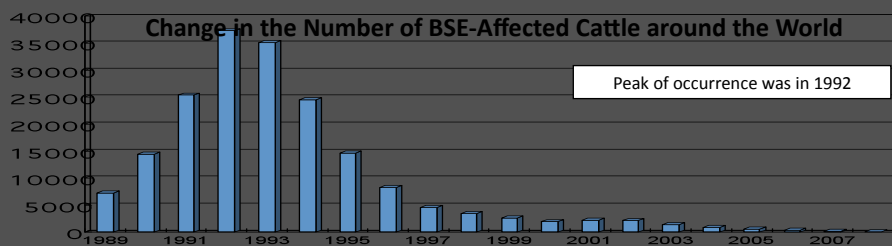
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Blocking of FcR suppress the intestinal invasion of scrapie agents

Ryuta Uraki*, Akikazu Sakudo*, Kosuke Michibata*, Yasuhisa Ano*, Juri Kono**, Masayoshi Yukawa**, Takashi Onodera*
 * University of Tokyo, * * Nihon University

5. Status of BSE Occurrence Abroad

•! Similar BSE countermeasures have been adopted world-widely. In recent years, the number of BSE-affected cattle in each country has decreased rapidly.

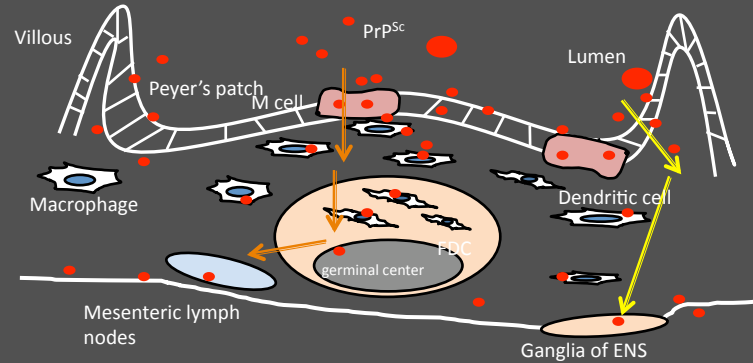


	1992	...	2001	2002	2003	2004	2005	2006	2007*1	2008*1	Total*1
Overall	37,316	...	2,215	2,179	1,389	878	561	329	169	23	190,355
Europe (excluding UK)	36	...	1,010	1,032	772	529	327	199	96	11	5,752
UK	37,280	...	1,202	1,144	611	343	225	114	67	10	184,551
US	0	...	0	0	0	0	1	1	0	0	2
Canada	0	...	0	0	2 ^{(*)2}	1	1	5	3	1	14 ^{(*)3}
Japan	0	...	3	2	4	5	7	10	3	1	35
Israel	0	...	0	1	0	0	0	0	0	0	1

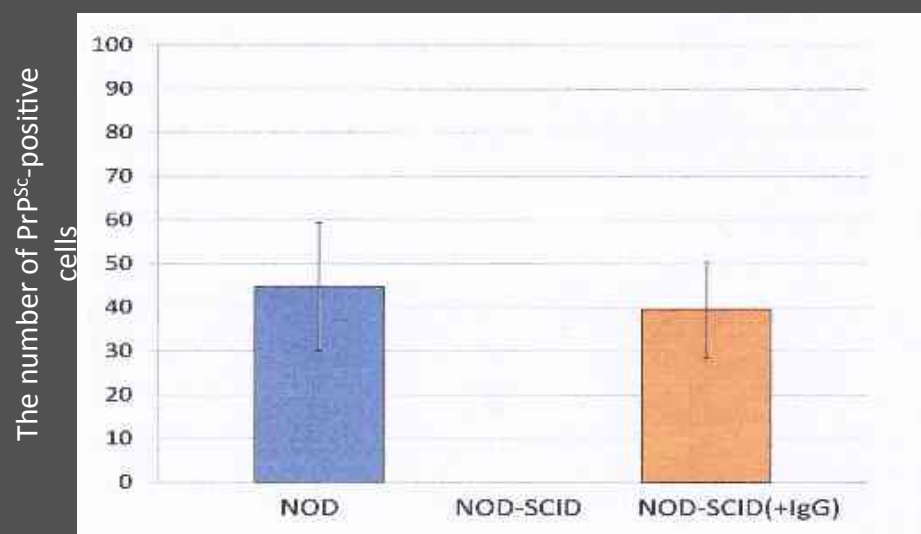
^{*2} One of these cases was identified in the US. ^{(*)3} The total number of Canadian cases includes one case of imported cow and one case firstly confirmed in the US (tested in December 2003).

Background (transmission of prion diseases)

- Oral transmissibility by PrP^{Sc} (issue in food safety)
- Invasion and dynamics in the intestines of PrP^{Sc} is little elucidated.
 - M cells on Peyer's patches or Villous epithelium



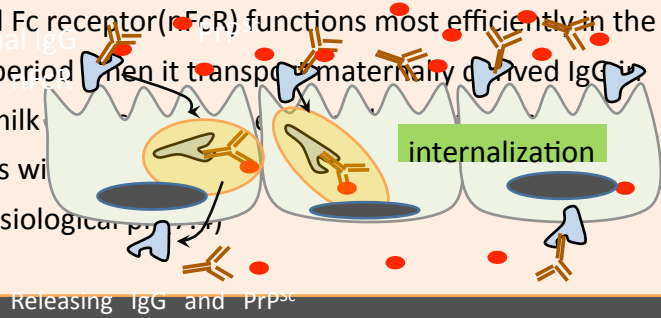
15 day-old-SCID mice (with IgG) PrP^{Sc} uptake in intestine



Background (function of neonatal Fc receptor)

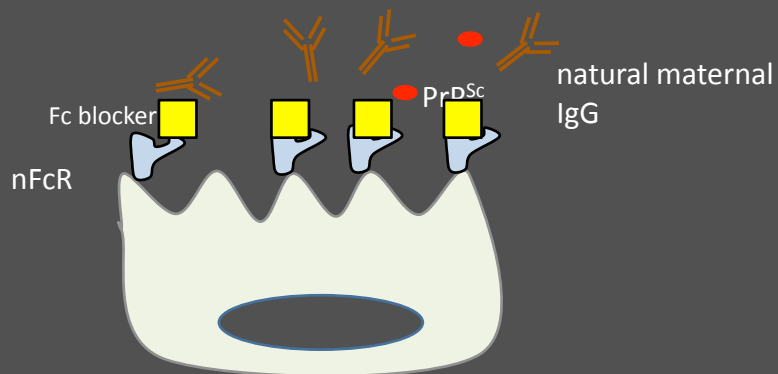
The neonatal Fc receptor (nFcR) functions most efficiently in the neonatal period when it transports maternally derived IgG from ingested milk.

IgG binds with high affinity to nFcR, but not at physiological pH.



Concept

When Fc receptors are blocked by compound, what happens in terms of incorporating PrP^{Sc}?



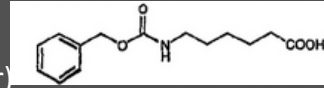
Materials and Methods (Administration and preparation of tissue specimens)

Animals

CD-1 or NOD mice (15-day -old)

Substance of administration and condition

- Z-ε-aminocaproic acid (Fc receptor blocker)
- IgG (5.0mg/ml in PBS)
- 10% brain homogenate infected with scrapie prions (Tsukuba1)
(Under the appropriate biosafety condition)



CD-1 mice (15-day -old)



Small intestine of CD-1

Materials and Methods (Administration and preparation of NOD mouse tissue specimens)

Euthanized and extirpation of intestine and spleen
① duodenum, ②③ jejunum, ④⑤ ileum

Fixed by immersion in 4 % paraformaldehyde

Technobit embedding

immunostaining



Technobit embedding

Materials and Methods
(Administration and preparation of tissue specimens)

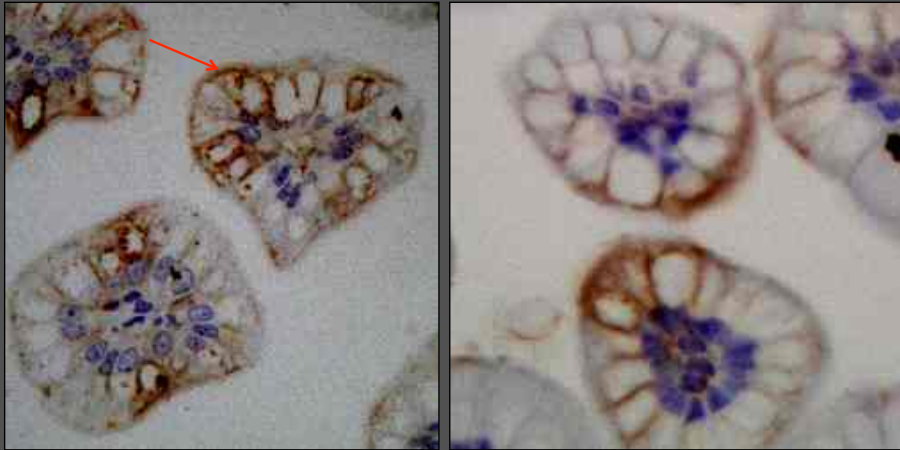
Fc receptor blocker	×	○	○	×	○	○
IgG	○	○ [†]	○ ^{††}	×	×	×
scrapie prions	×	×	×	○	○ [†]	○ ^{††}

† : IgG or prions was administrated 2h later the administration of Fc receptor blocker

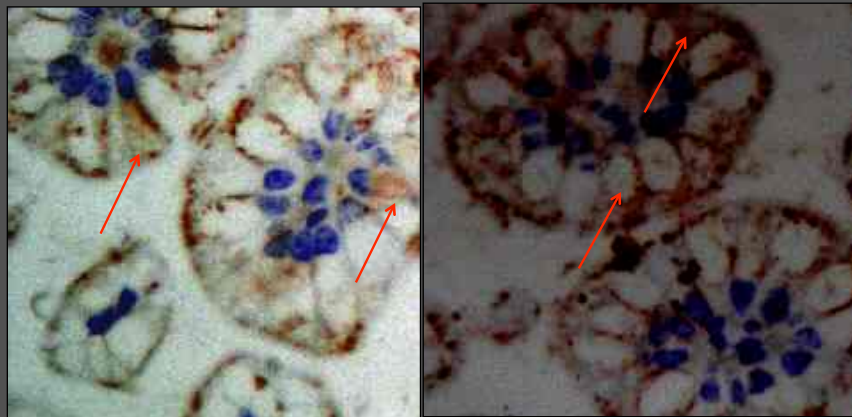
†† : IgG or prions was administrated with Fc receptor blocker

The number of positive cells in each microscopic visual fields was counted at five random points in the villous epithelium. Cell counts are expressed as the mean \pm SD of microscopic fields viewed at x400 magnification.

Intestinal invasion of PrPSc

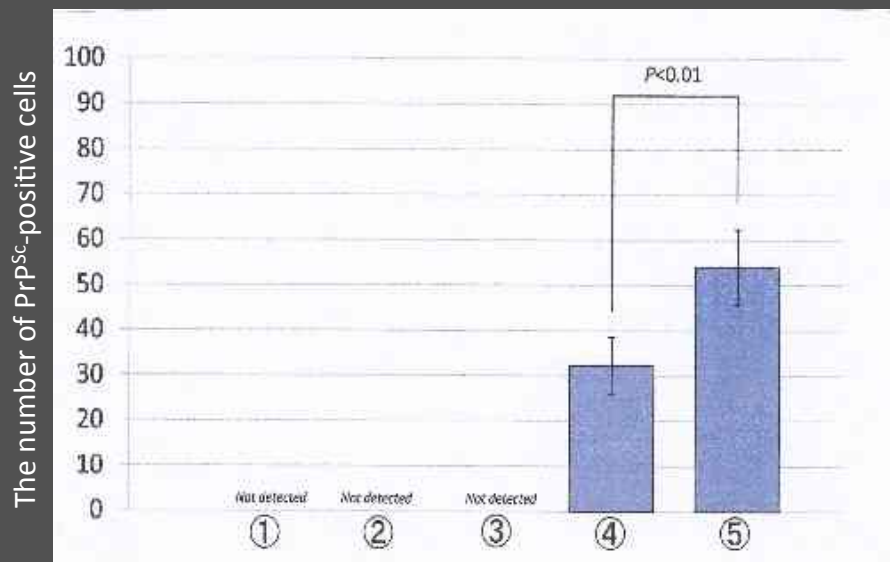


Intestinal invasion of IgG



Results

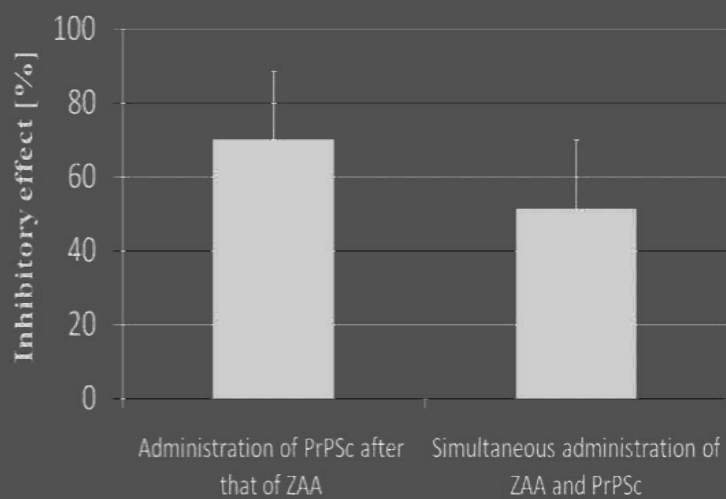
15 day-old-NOD mice, PrP^{Sc} uptake in intestine



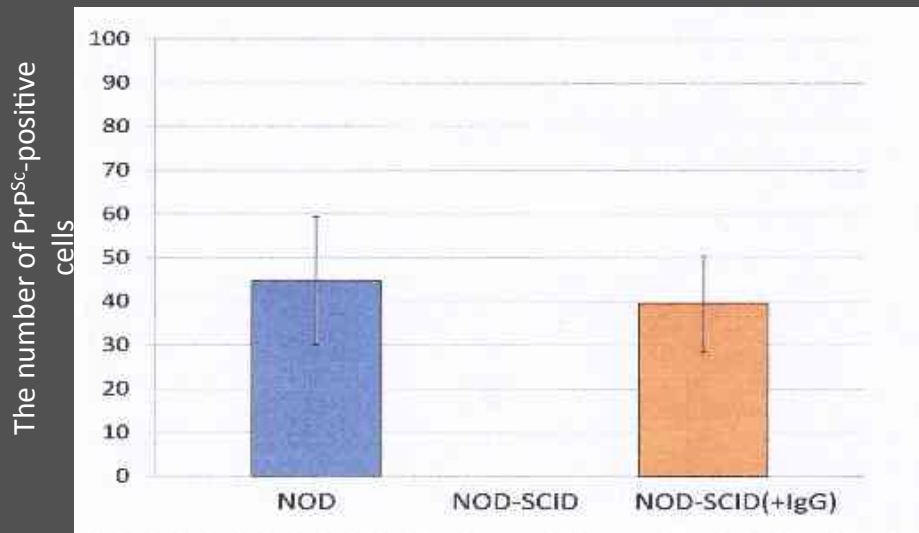
The inhibitory effect was calculated as following formula

$$\frac{\text{Percentage of ileal epithelial cells incorporating IgG or PrPSc with ZAA treatment}}{\text{Percentage of ileal epithelial cells incorporating IgG or PrPSc without ZAA treatment}} \times 100(\%)$$

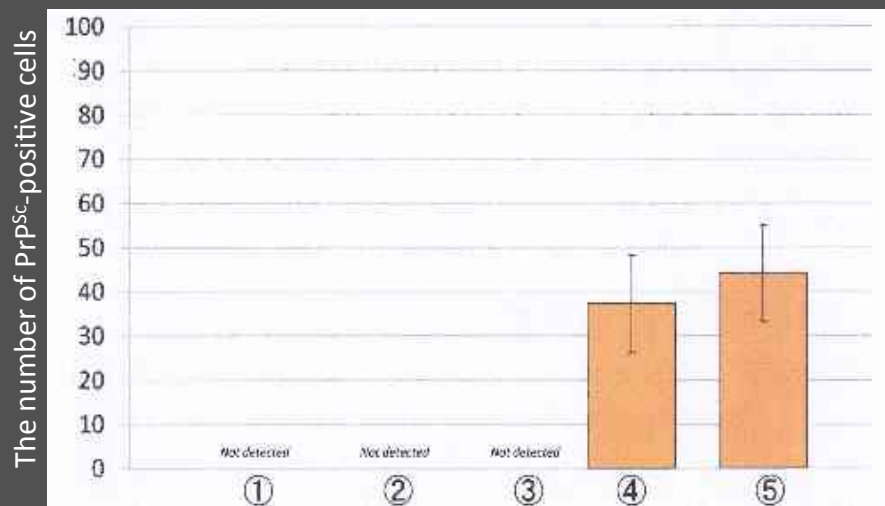
FcR blocker (Z-ε-aminocaproic acid) suppresses the intestinal invasion of scrapie agents in NOD mouse



15 day-old-SCID mice (with IgG) PrP^{Sc} uptake in intestine

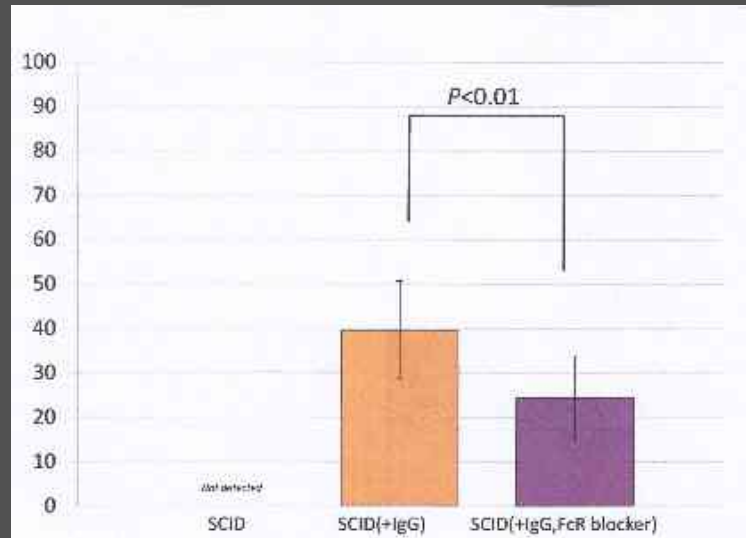


15 day-old-NOD SCID (with IgG) mice PrP^{Sc} uptake in intestine



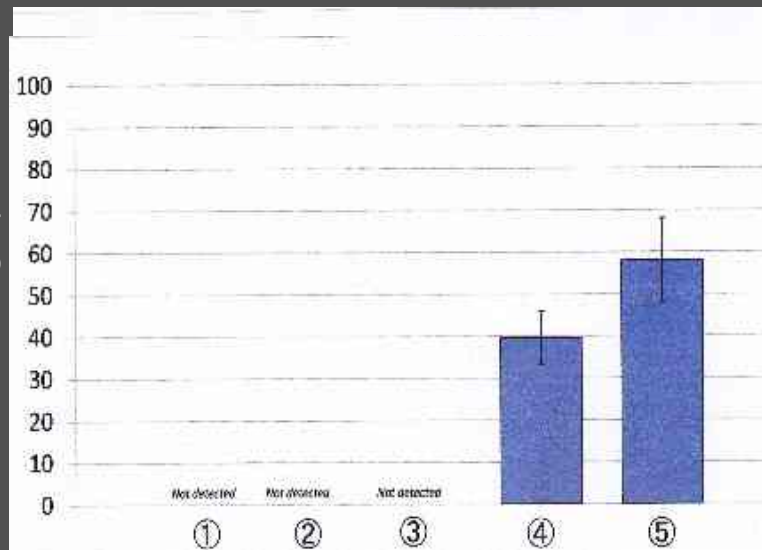
FcR blocker inhibit the incorporation of PrP^{Sc} in the NOD mouse ileum

The number of PrP^{Sc}-positive cells

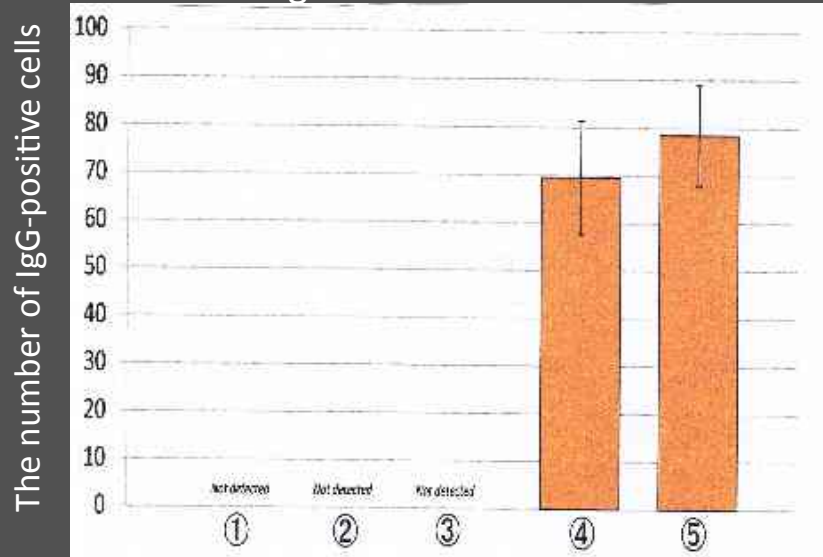


15 day-old-NOD mice with incorporation of IgG in the ileum

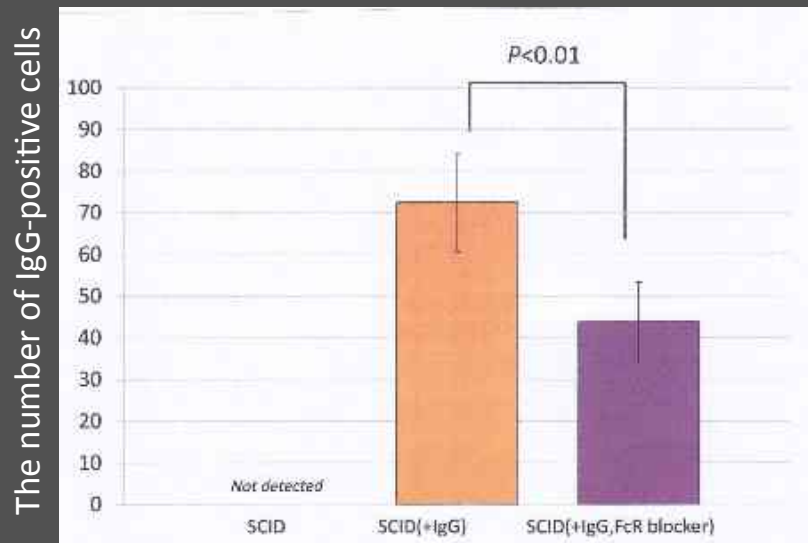
The number of IgG-positive cells



15 day-old-NOD SCID (+IgG) mice with incorporation of IgG in the ileum



FcR blocker inhibit the incorporation of IgG in the NOD mouse ileum

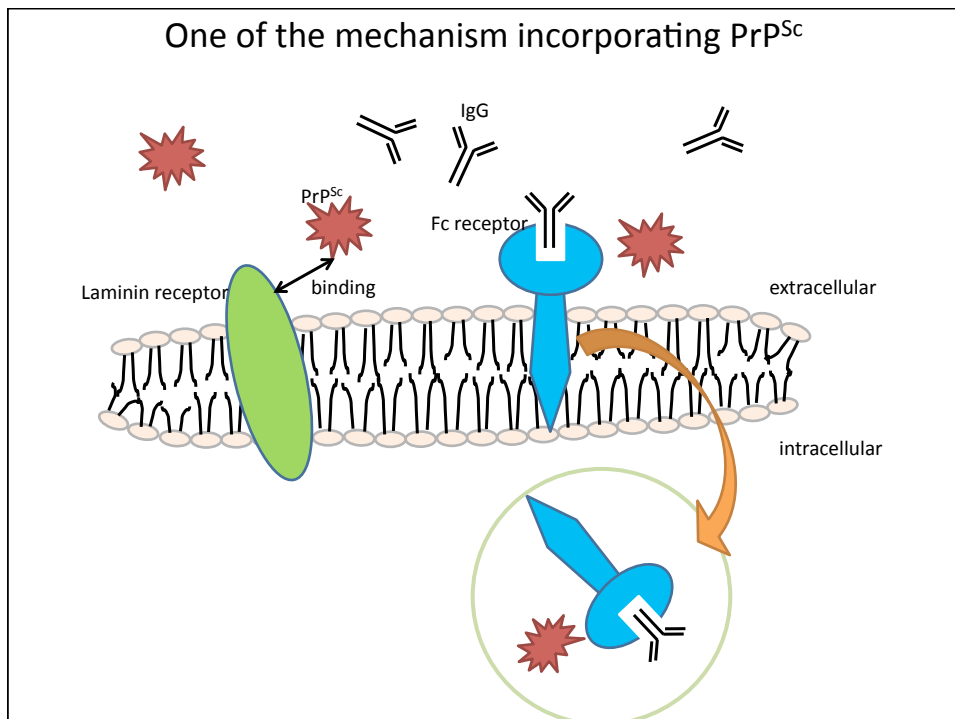


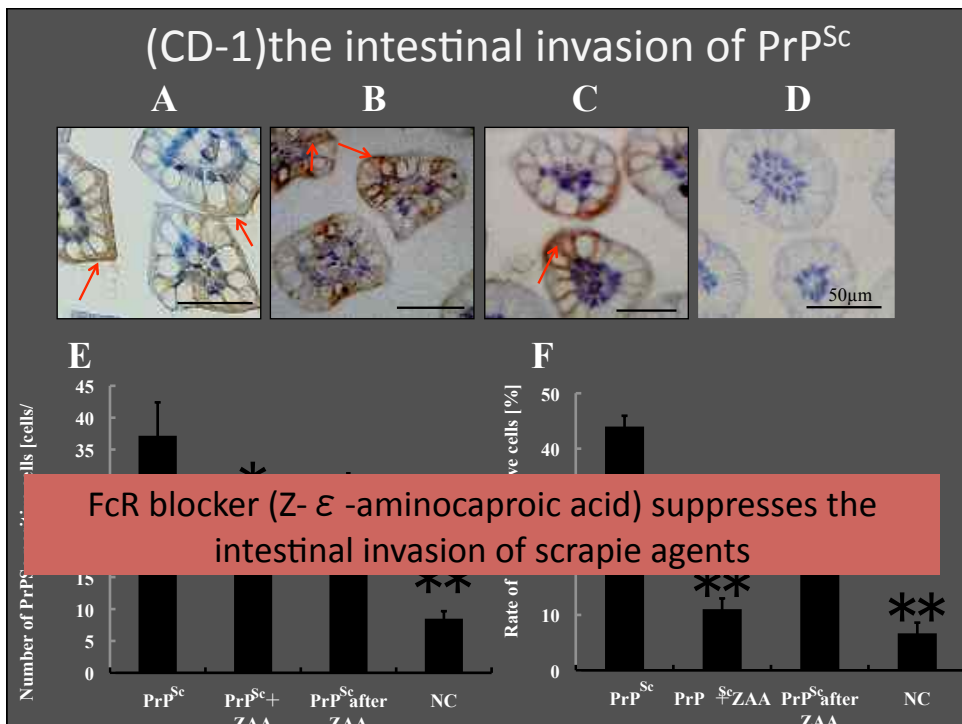
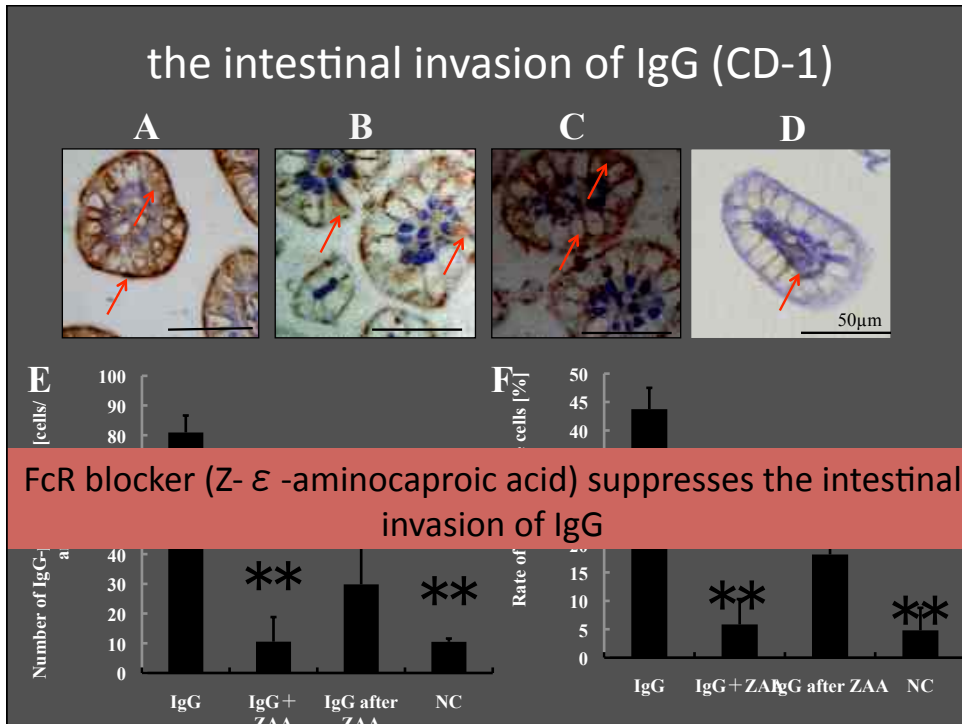
Conclusion

Fc receptors were blocked by FcR blocker

The incorporation of Prion was observed in latter part of ileum

Neonatal Fc receptor (nFcR) was associated with the incorporation of Prion in the latter part of ileum.





Background (transmission of prion diseases)

Maternal Igs or neonatal Fc receptor may affect the incorporation of PrP^{Sc} during lactation period.

