資料１

スクレイピーの
人への感染についての知見

1. スクレイピーの概要

- WHO
- OIE
- EFSA

2. 最近の科学的知見

- 2011年～2015年に報告された5報

1. スクレイピーの概要

WHO

Scrapie, another animal **TSE is endemic in some sheep and goat flocks** of Europe, Asia and North America (possibly elsewhere) with the exception of a small number of countries. During centuries of human and animal cohabitation, there has never been a demonstrated risk to humans from sheep scrapie.[1]

OIE

Scrapie **is not considered to pose a risk to human health**.

The recommendations in this chapter are intended to manage the animal health risks associated with the presence of the scrapie agent in sheep and goats. The chapter **excludes so-called 'atypical' scrapie** because this condition is clinically, pathologically, biochemically and epidemiologically unrelated to 'classical' scrapie, may not be contagious and may, in fact, be a spontaneous degenerative condition of older sheep.[2]

1. http://www.who.int/zoonoses/diseases/prion_diseases/en/
2. OIE - Terrestrial Animal Health Code 2015 - CHAPTER14.8. SCRAPIE Article 14.8.1.

1. スクレイピーの概要

EFSA

Scrapie in small ruminants is a disease described for several centuries. It was reported for the first time in UK in 1732 and affects both sheep and goats. Together these elements indicate that despite the protective measures implemented in 2001**, infectivity from Classical scrapie agents has continued to enter into the food chain**.[3]

There is no epidemiological evidence to suggest that Classical scrapie is zoonotic. The epidemiological data are **too limited to conclude whether the Atypical scrapie agent has a zoonotic potential**.[4]

3. http://www.efsa.europa.eu/en/topics/topic/transmissiblespongiformencephalopathies.htm
4. EFSA, SCIENTIFIC OPINION Joint Scientific Opinion on any possible epidemiological or molecular association between TSEs in animals and humans. EFSA Journal 2011;9(1)1945. #197

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Increased Susceptibility of Human-PrP Transgenic Mice to Bovine Spongiform Encephalopathy Infection following Passage in Sheep▽†

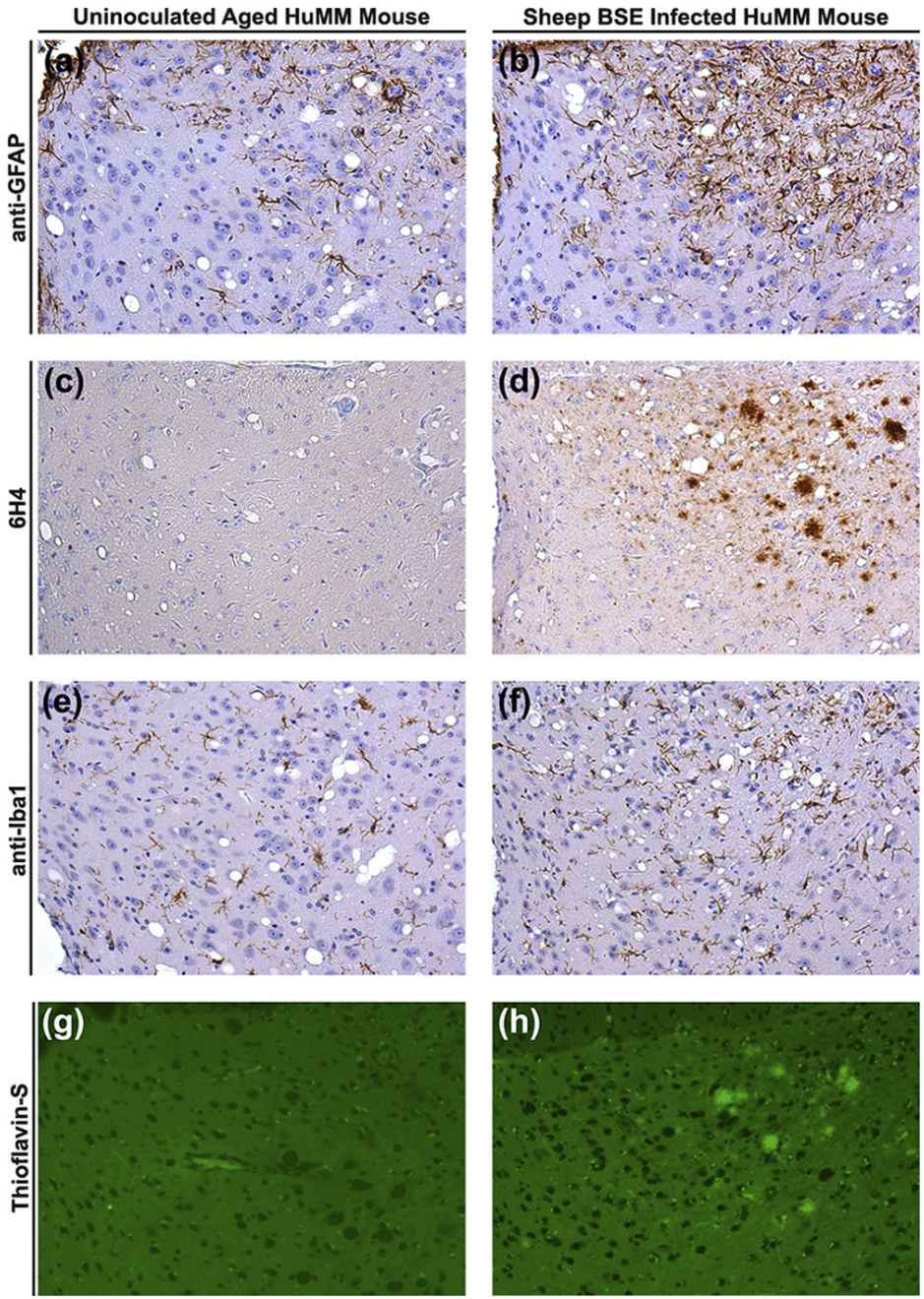
Chris Plinston,[1] Patricia Hart,[1] Angela Chong,[1] Nora Hunter,[1] James Foster,[1] Pedro Piccardo,[1,2] Jean C. Manson,[1] and Rona M. Barron[1]*

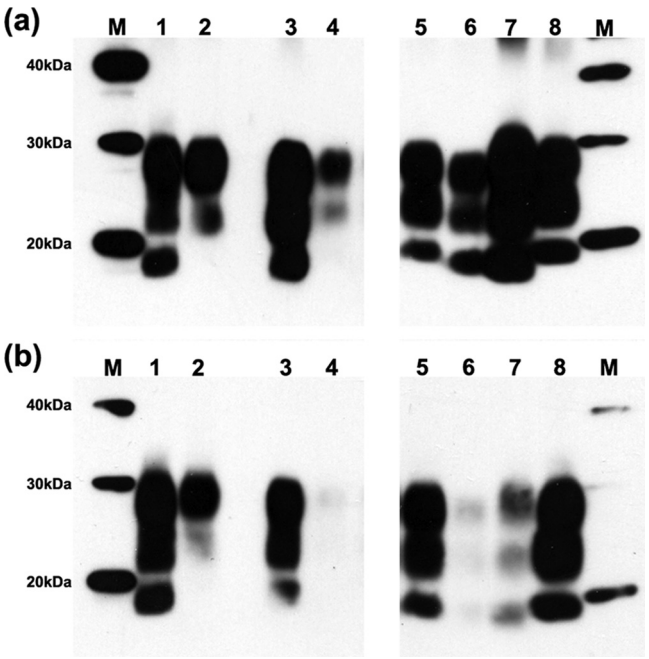
Neuropathogenesis Division, The Roslin Institute, and R(D)SVS, University of Edinburgh, Roslin, Midlothian, United Kingdom,[1] and Laboratory of Bacterial and TSE Agents, Food and Drug Administration, Rockville, Maryland[2]

TABLE 1. Transmission of cattle BSE, experimental sheep BSE, and natural scrapie to gene-targeted human and bovine transgenic mice

TSE isolate	Mouse line									
	129/Ola		Bov6		HuMM		HuVV		HuMV	
	Incubation time[a]	No. affected[b]	Incubation time	No. affected	Incubation time	No. affected	Incubation time	No. affected	Incubation time	No. affected
Cattle BSE (brain pool)	447 ± 27	8/8	551 ± 12[c]	22/22[c]	>765	0/18[c]	>793	0/22[c]	>749	0/23[c]
Sheep BSE inoculum 1	474 ± 22	11/11	564 ± 8	17/17	>812	1/20	>812	0/23	>812	0/23
Sheep BSE inoculum 2	403 ± 17	23/23	487 ± 3	24/24	>750	16/23	>650	0/23	>708	0/24
Natural scrapie 1	594, 705	2/15	>811	0/21	>685	0/24	>776	0/22	>671	0/23
Natural scrapie 2	510 ± 17	15/23	>647	0/24	>730	0/24	>710	0/24	>682	0/24

[a] Measured as days ± standard errors of the means and calculated from mice showing both clinical and pathological signs of TSE. >*n* represents the survival in days of the oldest mouse in groups where both clinical and pathological signs of disease were not observed in any animals.
[b] Number of mice showing TSE pathology (vacuolation and/or PrP deposition)/number of mice inoculated.
[c] Data are from Bishop et al. (4).


Uninoculated Aged HuMM Mouse
Sheep BSE Infected HuMM Mouse
anti-GFAP
6H4
anti-Iba1
Thioflavin-S
(a)
(b)
(c)
(d)
(e)
(f)
(g)
(h)


(a)
M 1 2 3 4 5 6 7 8 M
40kDa
30kDa
20kDa
(b)
M 1 2 3 4 5 6 7 8 M
40kDa
30kDa
20kDa

Chronic wasting disease and atypical forms of bovine spongiform encephalopathy and scrapie are not transmissible to mice expressing wild-type levels of human prion protein

Rona Wilson,[1] Chris Plinston,[1] Nora Hunter,[1] Cristina Casalone,[2] Cristiano Corona,[2] Fabrizio Tagliavini,[3] Silvia Suardi,[3] Margherita Ruggerone,[3] Fabio Moda,[3] Silvia Graziano,[4] Marco Sbriccoli,[4] Franco Cardone,[4] Maurizio Pocchiari,[4] Loredana Ingrosso,[4] Thierry Baron,[5] Juergen Richt,[6]† Olivier Andreoletti,[7] Marion Simmons,[8] Richard Lockey,[8] Jean C. Manson[1] and Rona M. Barron[1]

Table 1. Transmission of BASE, BSE-H, CWD and atypical scrapie to human and bovine PrP Tg mice

>*n*, Represents the survival in days of the oldest mouse in groups where pathological signs of disease were not observed in any animals. NA, Not applicable.

TSE isolate	Mouse line									
	HuMM		HuMV		HuVV		Bov6*		129/Ola*	
	Survival time	No. affected	Survival time	No. affected	Survival time	No. affected	Survival time	No. affected	Survival time	No. affected
BASE (Roslin)	>687	0/24	>672	0/24	>763	0/24	547 ± 18†	24/24‡	>687	1/24‡
BASE (Milan)	>753	0/23	>700	0/23	>726	0/19	NA	NA	NA	NA
BASE#1 (Rome)	>633	0/19	>680	0/14	>707	0/17	NA	NA	NA	NA
BASE#2 (Rome)	>604	0/16	>854	0/29	>740	0/20	NA	NA	NA	NA
BSE-C (Rome)	>592	0/14	>856	0/15	>509	0/13	NA	NA	NA	NA
BSE-H	>722	0/24	>708	0/24	>708	0/24	561 ± 15†	17/23‡	675 ± 19†	5/23‡
CWD	>680	0/24	>730	0/24	>722	0/24	>716	0/23	457, 707	2/24‡
Sheep passaged atypical scrapie	>693	0/24	>693	0/24	>693	0/24	>693	0/24	>693	0/24
Atypical scrapie ARR/ARR1	>651	0/23	>724	0/21	>829	0/24	>781	0/24	>753	0/24
Atypical scrapie AHQ/AHQ1	>822	0/24	>718	0/24	>682	0/22	>757	0/23	>710	0/11
Atypical scrapie ARR/ARR2	>722	0/24	>744	0/24	>841	0/23	>756	0/22	>673	0/12
Atypical scrapie AHQ/AHQ2	>786	0/22	>768	0/23	>700	0/24	>805	0/24	>779	0/21
Atypical scrapie AFRQ/AFRQ1	>815	0/24	>717	0/23	>759	0/23	>757	0/23	>772	0/24
Atypical scrapie AFRQ/AFRQ2	>750	0/23	>722	0/23	>756	0/24	>726	0/24	>756	0/12

*Results for BASE and H-type BSE inoculations into Bov6 mice and 129/Ola mice have previously been published (Wilson *et al.*, 2012).
†Measured as days ± SEM and calculated from mice showing pathological signs of disease (vacuolation and/or PrP deposition).
‡Number of mice showing pathological signs of disease (vacuolation and/or PrP deposition)/number of mice inoculated.

Atypical Scrapie Prions from Sheep and Lack of Disease in Transgenic Mice Overexpressing Human Prion Protein

Jonathan D.F. Wadsworth, Susan Joiner, Jacqueline M. Linehan, Anne Balkema-Buschmann, John Spiropoulos, Marion M. Simmons, Peter C. Griffiths, Martin H. Groschup, James Hope, Sebastian Brandner, Emmanuel A. Asante, and John Collinge

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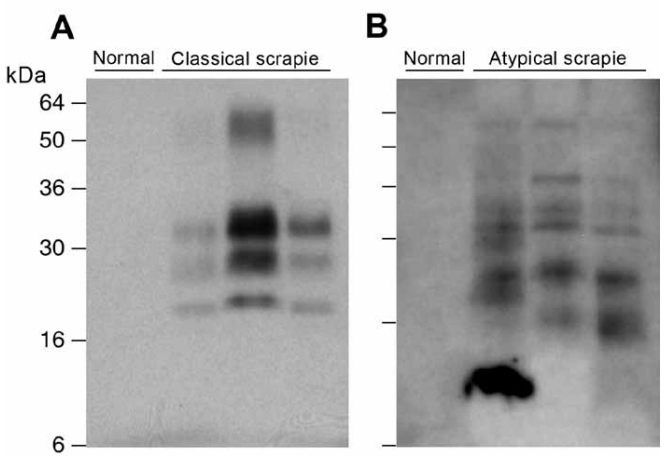
Table 2. Survival times of transgenic human PrP mice after inoculation of ovine prions*

		Transmission data			
		129MM Tg35c mice		129VV Tg152c mice	
Source code	Prion agent	Attack rate†	Survival, d‡	Attack rate†	Survival, d‡
AHVLA/SE1919/0077	Classical scrapie	0/20	551, 551, 583, 615–666 (17)	0/16	301, 344, 344, 364, 386, 428, 475, 519, 540, 543, 600–601 (6)
AHVLA/SE1919/0080	Classical scrapie	0/19	580, 586, 586, 620–666 (16)	0/14	211, 336, 364, 364, 379, 519, 601–602 (8)
FLI 1/06	Classical scrapie	0/15	426, 475, 628–728 (13)	0/17	364, 497, 498, 517, 547, 559, 571, 595, 603–673 (9)
FLI 83/04	Classical scrapie	0/15	270, 307, 311, 335, 349, 353, 635–672 (9)	0/16	227, 300, 335, 440, 479, 510, 600–650 (10)
FLI 107/04	Classical scrapie	0/17	382, 382, 459, 573, 574, 578, 606–636 (11)	0/13	227, 228, 476, 606–706 (10)
AHVLA/SE1850/0001	Atypical scrapie	0/18	213, 332, 437, 537, 537, 621–656 (13)	0/18	255, 318, 385, 397, 402, 403, 452, 453, 493, 518, 528, 538, 543, 552, 633–647 (4)
AHVLA/SE1850/0009	Atypical scrapie	0/18	440, 606–635 (17)	0/15	293, 334, 403, 404, 419, 420, 426, 444, 584, 637–651 (6)
FLI S7/06	Atypical scrapie	0/16	498, 610–659 (15)	0/14	539, 545, 630–673 (12)
FLI 14/06	Atypical scrapie	0/18	538, 540, 545, 572, 601–728 (14)	0/15	313, 363, 489, 510, 592, 602–673 (10)
FLI 26/06	Atypical scrapie	0/14	547, 553, 643–659 (12)	0/14	435, 446, 554, 571, 608–673 (10)
AHVLA/SE1929/0877	Ovine BSE	0/16	315, 316, 348, 459, 557, 581, 620–659 (10)	0/18	358, 363, 369, 382, 385, 440, 468, 476, 532, 550, 574, 600–602 (7)
AHVLA/SE1945/0032	2nd passage ovine BSE	1/19	337, 337, 434, 472, 517, 524, 616–661 (13)	0/17	331, 331, 381, 386, 388, 388, 525, 527, 542, 562, 603–608 (7)

*PrP, prion protein; AHVLA, Animal Health and Veterinary Laboratories Agency; FLI, Friedrich-Loeffler-Institut; BSE, bovine spongiform encephalopathy.
†All mice were inoculated with 30 μL of 1% (w/v) brain homogenate. Attack rate is defined as the total number of clinically affected and subclinically infected mice as a proportion of the number of inoculated mice. Subclinical prion infection was assessed by immunohistochemical examination of brain for abnormal PrP deposition and for recipients of AHVLA inocula by sodium phosphotungstic acid precipitation of 250 μL 10% brain homogenate and analysis for PrP^{Sc} by proteinase K digestion and immunoblotting.
‡The interval between inoculation and culling because of intercurrent illness, senescence, or termination of the experiment in days. Death dates of individual mice are shown together with the range for mice surviving beyond 600 d with the number of mice in this range shown in parentheses. Mice culled with postinoculation periods of ≤200 d due to intercurrent illness (all confirmed negative for prion infection) were not included in calculating attack rates.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B
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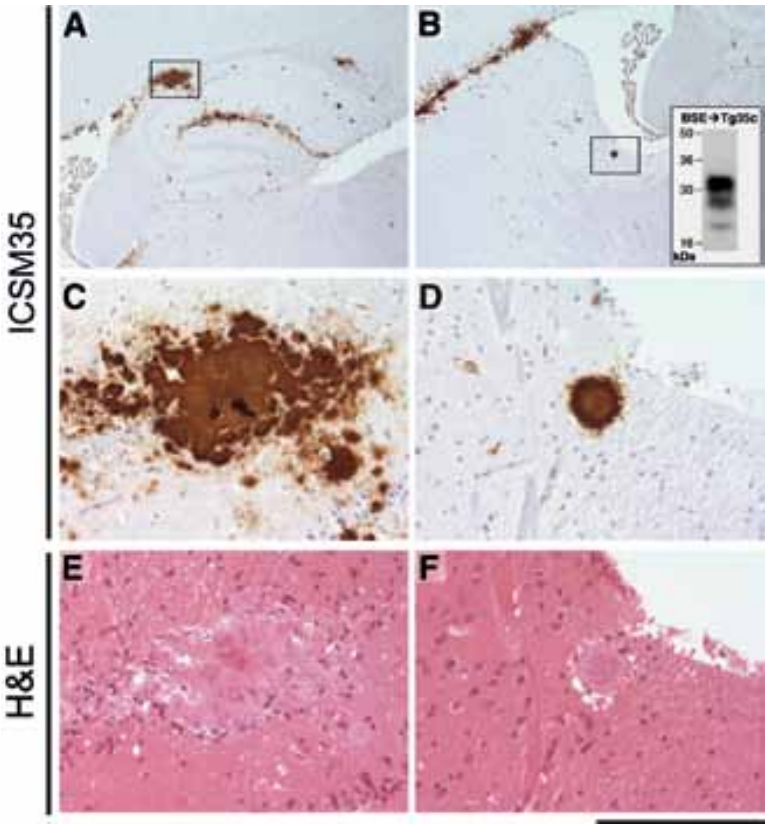
Atypical scrapie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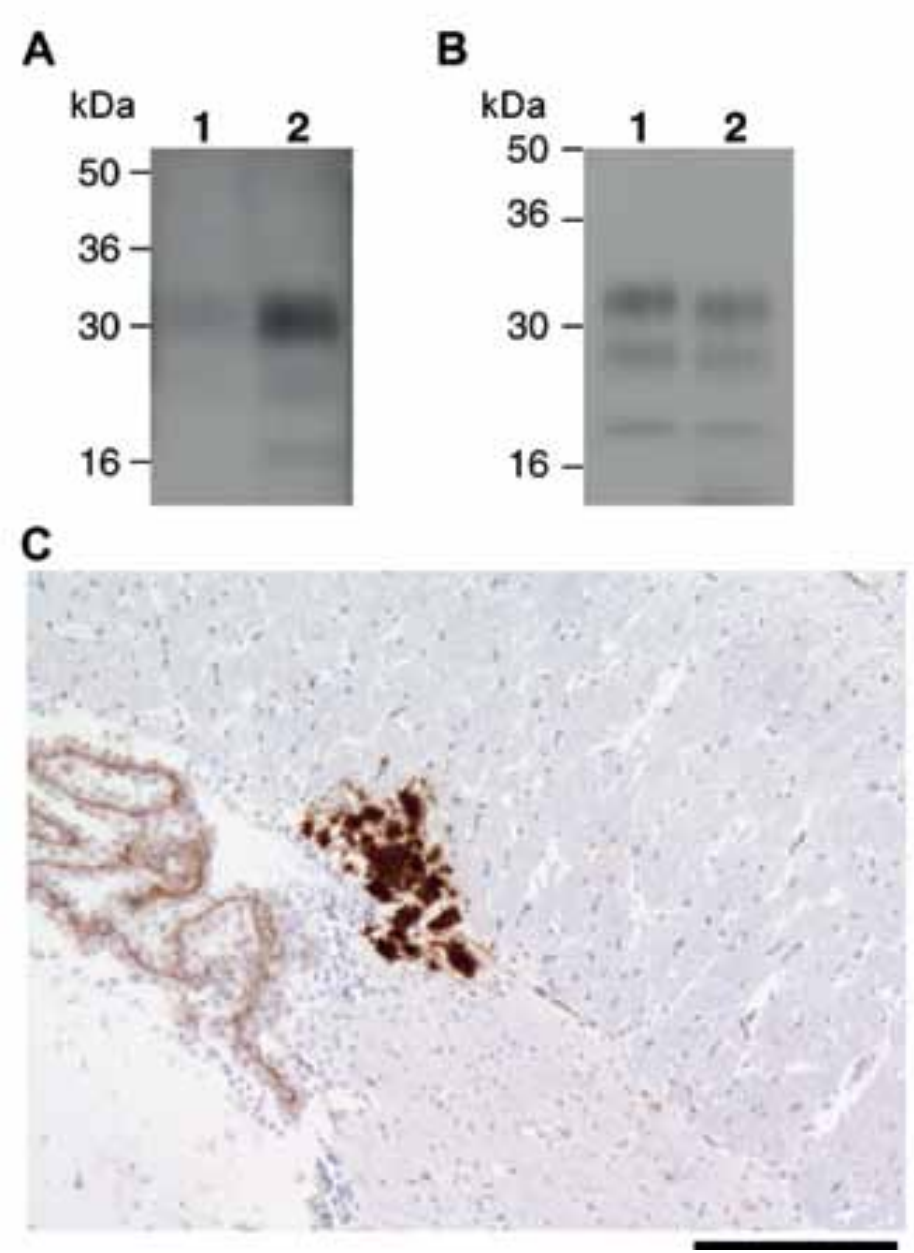
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ARTICLE

Received 7 Aug 2014 | Accepted 10 Nov 2014 | Published 16 Dec 2014

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nature COMMUNICATIONS

Evidence for zoonotic potential of ovine scrapie prions

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Table 1 | Intracerebral inoculation of tgHu mice with a panel of human, bovine and ovine prion isolates.

	Isolate	Origin	Tg Met/Met$_{129}$				TgMet/Val$_{129}$				TgVal/Val$_{129}$			
			Passage 1		Passage 2		Passage 1		Passage 2		Passage 1		Passage 2	
			Positive mice	Incubation (d.p.i. ± s.d.)	Positive mice	Incubation (d.p.i. ± s.d.)	Positive mice	Incubation (d.p.i. ± s.d.)	Positive mice	Incubation (d.p.i. ± s.d.)	Positive mice	Incubation (d.p.i. ± s.d.)	Positive mice	Incubation (d.p.i. ± s.d.)
	sCJD MM1	Hu	6/6	219 ± 17	6/6	239 ± 8	6/6	243 ± 14	6/6	260 ± 13	6/6	327 ± 19	6/6	286 ± 16
	sCJD VV2	Hu	6/6	618 ± 81	6/6	509 ± 41	6/6	588 ± 74	6/6	594 ± 86	6/6	168 ± 12	6/6	169 ± 12
	vCJD	Hu	6/6	595 ± 25	6/6	581 ± 45	2/6	758, 801	6/6	615 ± 65	0/6	>750	0/6	>750
	BSE	Bov	0/6	>750	3/6	572 ± 64	0/6	>750	NA		0/6	>750	0/6	>750
	BSE	Bov	1/6	739	6/6	633 ± 32	0/6	>750	NA		0/6	>750	0/6	>750
●	MF17	Ov	0/6	>750	NA		2/6	743*, 760*	3/6	343, 374, 665	0/6	>750	0/6	>700
●	PS09	Ov	0/6	>750	1/6	432	0/6	>750	0/6	>600	0/6	>750	0/6	>700
●	PS21	Ov	0/6	>750	2/6	369,579	0/6	>750	0/6	>700	0/6	>750	0/6	>700
○	PS48	Ov	0/6	>750	0/6	>750	0/6	>750	0/6	>700	0/6	>750	0/5	>700
○	PS42	Ov	0/6	>750	1/6	475	0/6	>750	0/6	>700	0/6	>750	0/6	>700
●	PS310	Ov	0/6	>750	NA		0/6	>750	NA	-	0/6	>750	NA	
	Negative brain	Hu	0/12	>750	0/12	>750	0/12	>750	0/6	>650	0/12	>750	0/6	>750
		Ov	0/12	>750	0/12	>750	0/12	>750	0/6	>650	0/12	>750	0/6	>750
	PBS control		0/18	>800	0/12	>650	0/12	>750	0/6	>650	0/12	>750	0/6	>750

Transgenic mice that express the Met$_{129}$, Val$_{129}$ human PrP and their cross bred were inoculated intra-cerebrally (20 µl per mouse) with a 10% brain homogenate from (i) sporadic Creutzfeldt-Jakob (sCJD) variant Creutzfeldt Jakob (vCJD) methionine homozygous patients, (ii) bovine (Bov) spongiform encephalopathy-affected cattle, (iii) ovine (Ov) scrapie isolates (MF17, PS09, PS21, PS48, PS42 and PS310). After first passage, clinically affected or asymptomatic mice that survived >500 d.p.i. were pooled and used for second passage in the same line. Mice were considered positive when abnormal PrP deposition was detected in the brain.

Incubation periods (days post inoculation: d.p.i.) are shown as mean ± s.d. except when <50% of mice were found to be PrP^{res}-positive. In that latter case, the incubation period of PrP^{res}-positive mice is individually presented. Control mice were inoculated with negative brain tissue or PBS controls. sCJD and scrapie isolates were inoculated into mice in different rooms of the animal facilities. (NA): still ongoing bioassay, results not available.

*Indicates PrP^{res} and found dead animals (asymptomatic).

●ARQ/ARQ ○VRQ/VRQ

Table 2 | Intracerebral inoculation of transgenic mice that express human PrP with ovine scrapie isolates previously adapted in bovine PrP transgenic mice.

Isolate	Origin	First passage		Second passage			
		Tg Met_{129}		Tg Met_{129}		Tg Val_{129}	
		Positive mice	Incubation (d.p.i. ± s.d.)	Positive mice	Incubation (d.p.i. ± s.d.)	Positive mice	Incubation (d.p.i. ± s.d.)
sCJD MM1	**Hu**	**6/6**	219 ± 17	**6/6**	239 ± 8	**6/6**	298 ± 10
sCJD VV2	**Hu**	**6/6**	618 ± 81	**6/6**	509 ± 41	**6/6**	182 ± 9
vCJD	**Hu**	**6/6**	595 ± 25	**6/6**	581 ± 45	**0/6**	> 750
PS48	**TgBov**	**1/6**	453	**6/6**	230 ± 16	**6/6**	305 ± 4
PS310	**Tg Bov**	**1/6**	630	**5/5**	492 ± 27	**6/6**	208 ± 5
PS09	**Tg Bov**	**2/6**	407, 700*	**NA**		**NA**	
PS21	**Tg Bov**	**1/6**	499	**NA**		**NA**	

Tg Met_{129} mice were intracerebrally challenged with scrapie isolates (PS48, PS310, PS09, PS21) that had previously adapted into bovine PrP transgenic mice (two successive passages). In groups inoculated with PS48 and PS310 scrapie isolate one symptomatic $TgMet_{129}$ (showing abnormal PrP accumulation in its brain) was selected and its brain used for inoculating $TgMet_{129}$ and $TgVal_{129}$. Incubation periods (days post inoculation: d.p.i.) are shown as mean ± s.d. NA: still ongoing bioassay, results not available.
*Indicates PrP^{res}positive and found dead animals (asymptomatic).

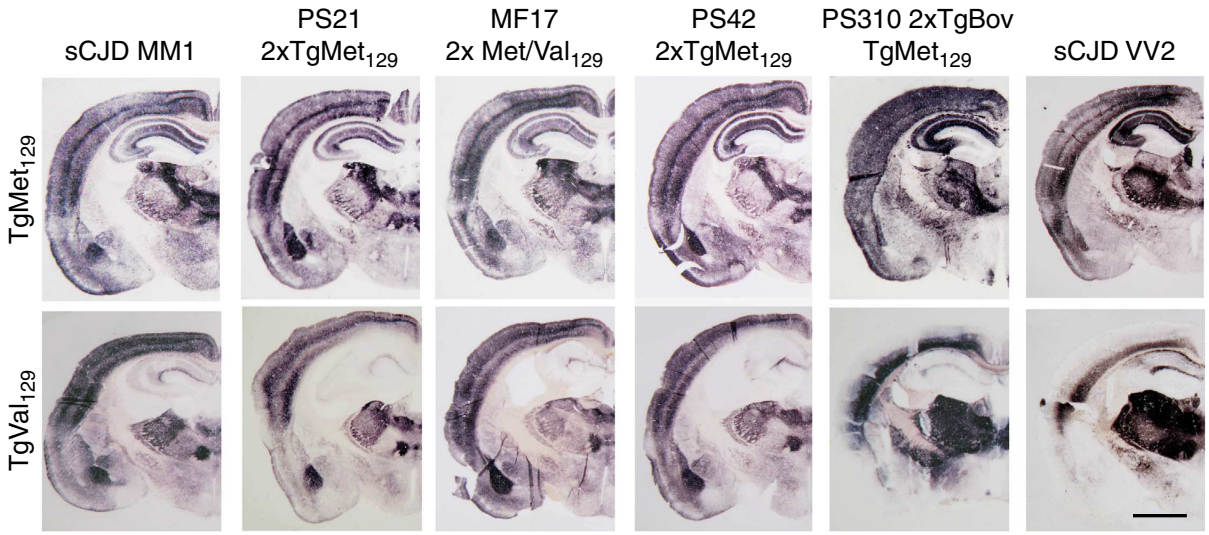
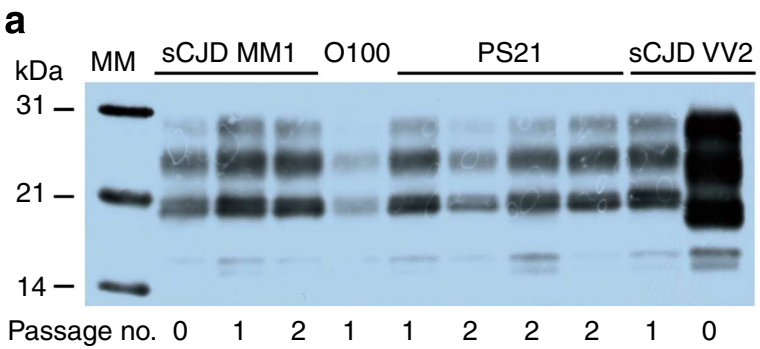
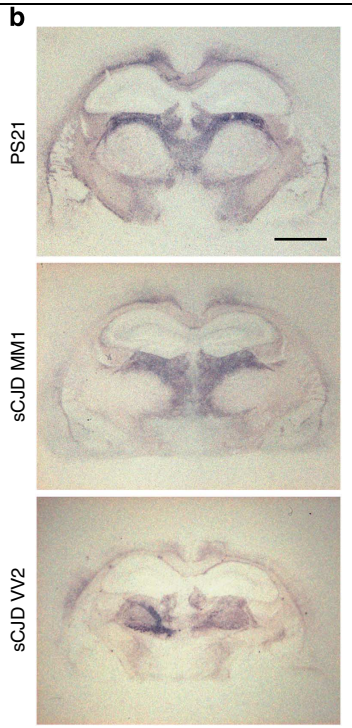


Table 4 | Intracerebral inoculation of tg650 transgenic mice with a panel of sheep scrapie isolates.

Isolate	Origin	Tg 650			
		Passage 1		Passage 2	
		Positive mice	Incubation (d.p.i. ± s.d.)	Positive mice	Incubation (d.p.i. ± s.d.)
sCJD MM1	**Hu**	**6/6**	177 ± 17	**4/4**	153 ± 3
sCJD VV2	**Hu**	**6/6**	566 ± 21	**6/6**	433 ± 18
vCJD	**Hu**	**8/8**	512 ± 15	**7/7**	581 ± 45
BSE	**Bov**	**2/6**	627; 842*	**6/7**	568 ± 65
PS21	**ov**	**1/8**	926*	**11/11**	180 ± 8
0100	**ov**	**1/6**	595*	**NA**	
PS310	**ov**	**0/9**	>750	**0/15**	>750
PS48	**ov**	**0/6**	>750	**NA**	
Healthy brain	**Hu**	**0/9**	>750	**0/6**	>750
	Ov	**0/6**	>750	**0/6**	>750

Tg650 mice that are transgenic for Met_{129} human PrP were inoculated intra-cerebrally (20 µl per mouse) with 10% brain homogenate from challenged with 10% brain homogenate from (i) sporadic Creutzfeldt-Jakob (sCJD) and variant Creutzfeldt Jakob (vCJD) patients, (ii) bovine (Bov) spongiform encephalopathy-affected cattle, (iii) ovine (Ov) scrapie isolates (PS21, O100, PS48 and PS310). After first passage, clinically affected or asymptomatic mice that survived >500 d.p.i. were pooled and used for second passage in the same mouse line. Mice were considered positive when abnormal PrP deposition was detected in the brain. Incubation periods (days post inoculation: d.p.i.) are shown as mean ± s.d., except when <50% of mice were found positive. In the latter case, the incubation periods of the positive mice are individually presented. Data in italics have been described in previous publications. NA: still ongoing bioassay, results not available.
*Indicates abnormal PrP positive and found dead animals (asymptomatic).





Transmission of scrapie prions to primate after an extended silent incubation period

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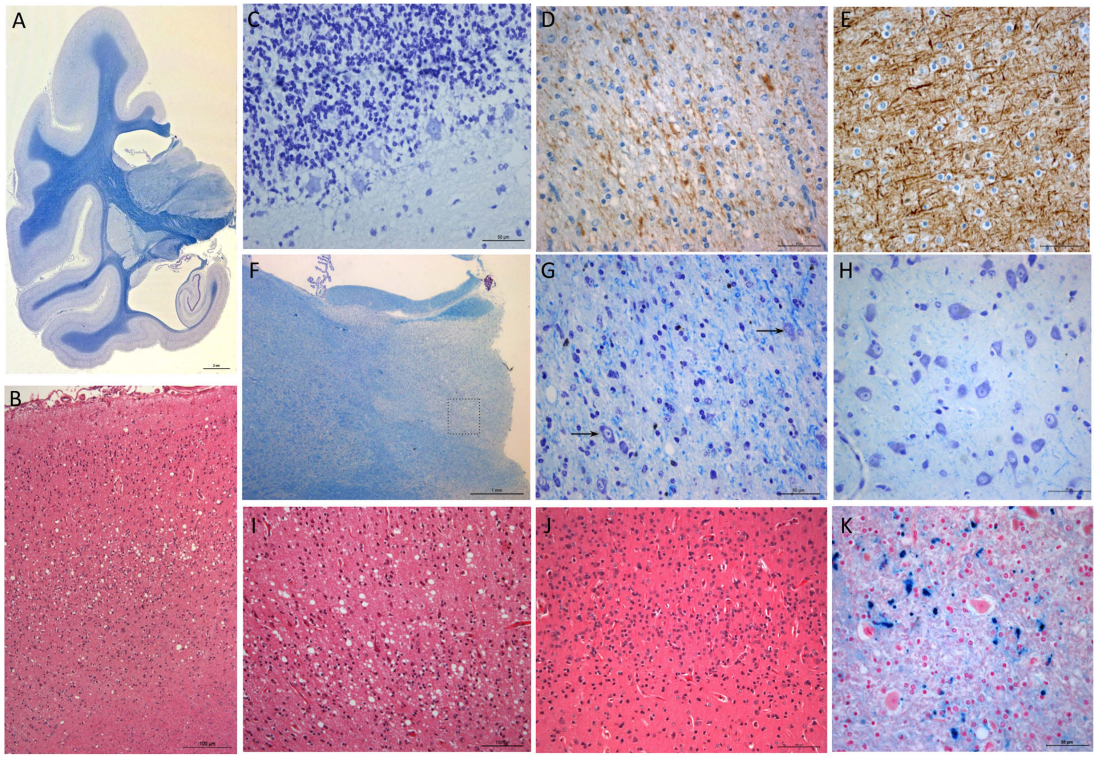
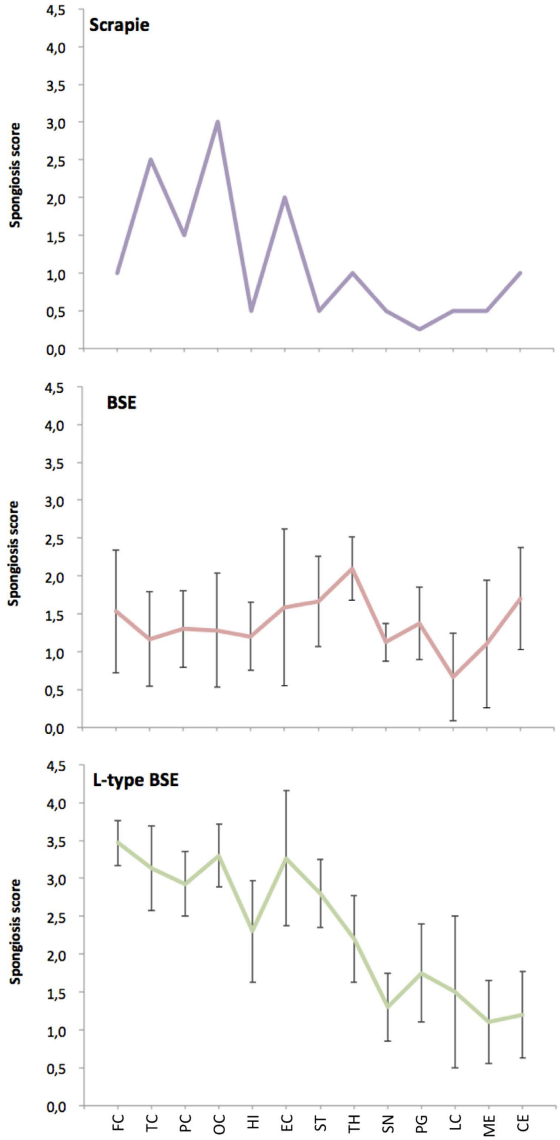
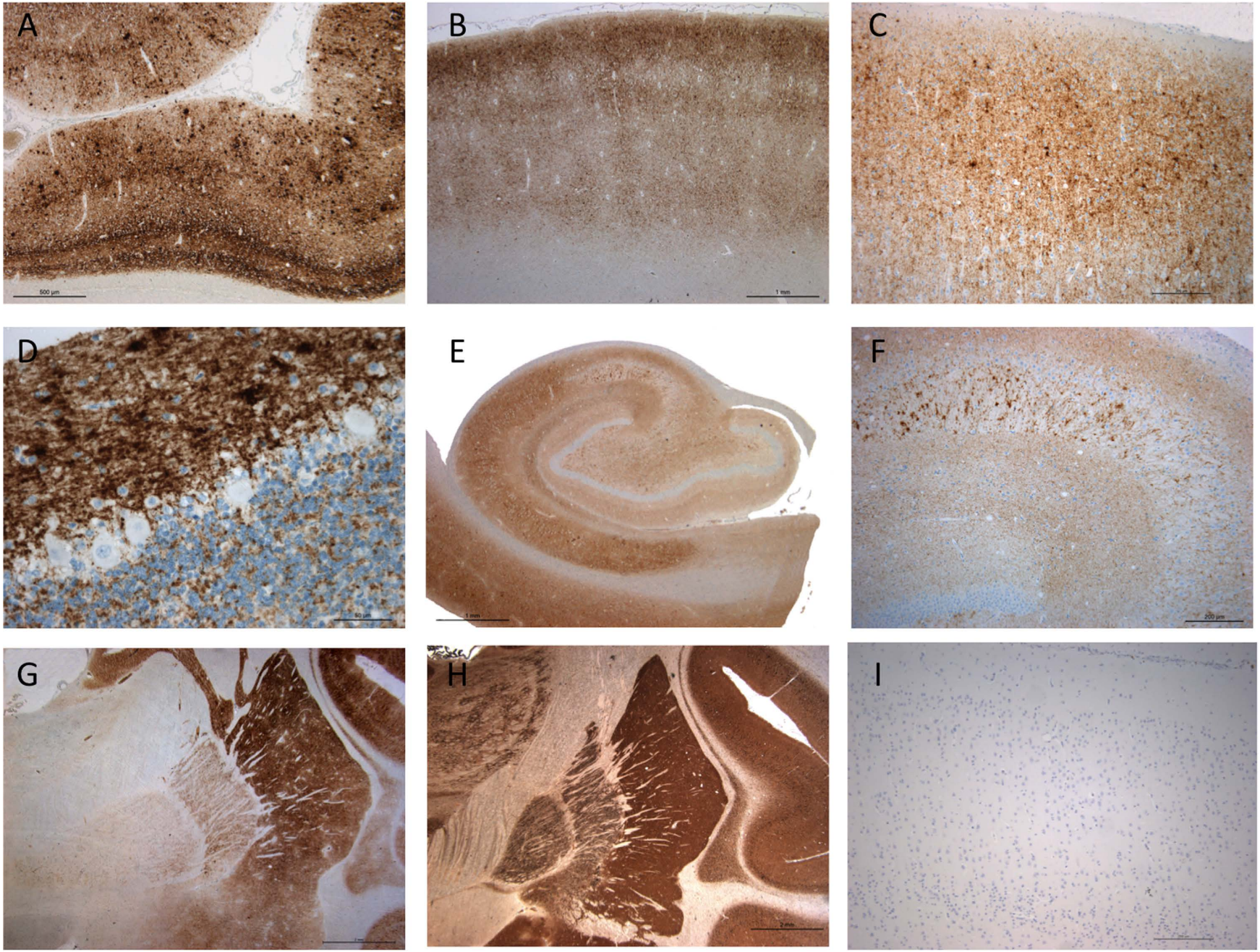
SCIENTIFIC REPORTS | 5:11573 | DOI: 10.1038/srep11573





最近の科学的知見 (5) #788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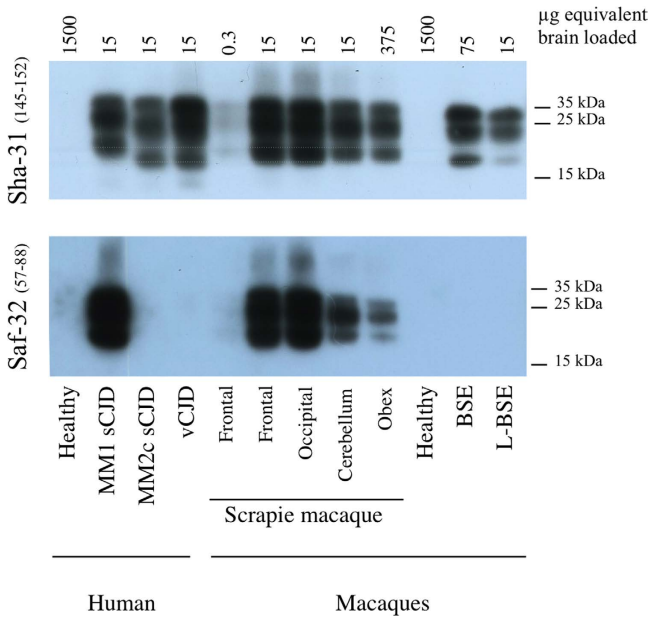

Prion isolate	Route	Host species	16 g	5 g	500 mg	100 mg	50 mg	40 mg	25 mg	20 mg	2.5 mg	0.5 mg	0.05 mg	0.005 mg
c-BSE	oral	Cattle	44-54 [1]	52-62 [1] 63 [2]	> 70 (0/6)									
c-BSE	i.c.	Cattle				34-37 (4/4)	31-49 [3] (6/6)			35-59 [4] (3/3)		47-93 (3/4)	85 (1/3)	> 140 (0/4)
L-type BSE	i.c.	Cattle							26 [5]	24-25 [6]	25 [*]			
Scrapie	i.c.	Sheep							118					
Nor98	i.c.	Sheep						> 87 [*]						
MD CWD	i.c.	Cattle						> 87 [*]						
WTD CWD	i.c.	Cattle						> 87 [*]						
WTD CWD	i.c.	White-tailed deer						> 87 [*]						
H-type BSE	i.c.	Cattle							> 122					
Controls		*Non-inoculated*						*> 84 - 115 - 171 - 222*						