SUPPLEMENTARY MATERIAL

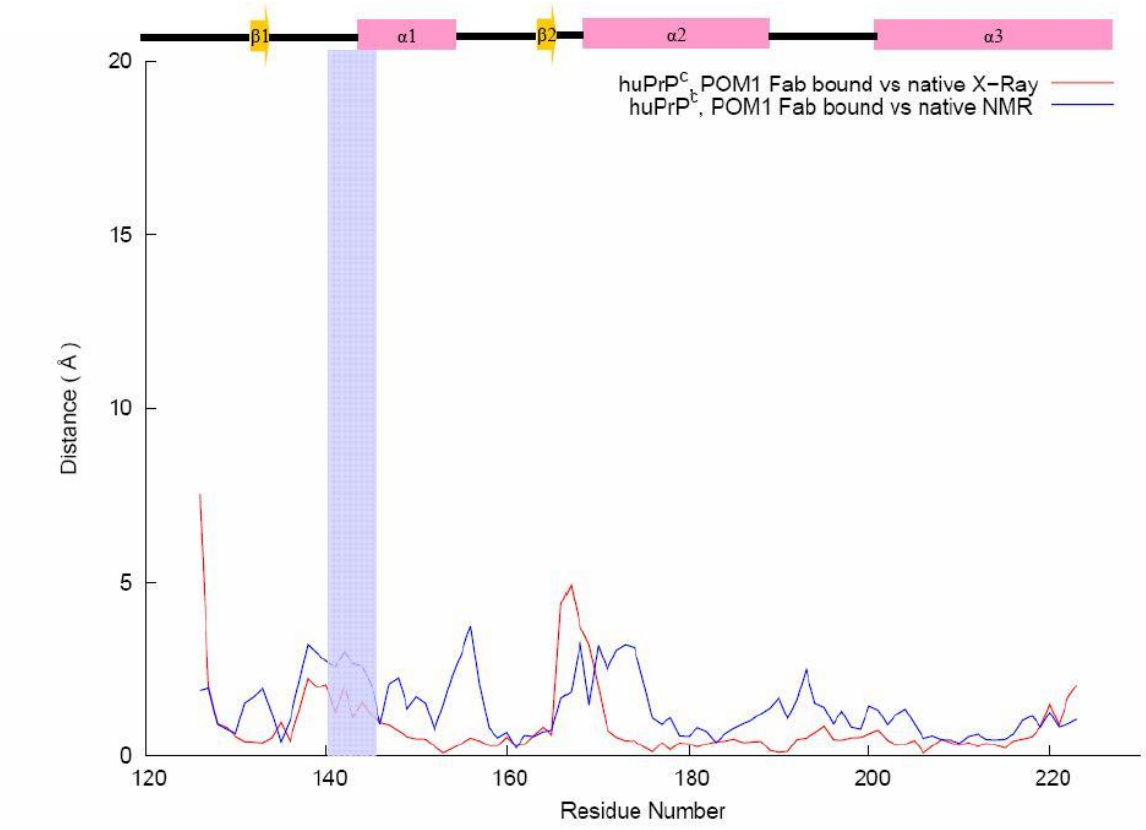
Supplementary Table S1. Protein geometry.

Protein geometry	Rotamer outlier	2.77
	Ramachandran outliers	0.19%
	Ramachandran favored	96.93%
	Cβ deviations >0.25	0
	Residues with bad bonds:	0
	Residues with bad angles:	0.76%

Supplementary Table S2. Shape complementarity statistics

POM1 Fab:huPrP^{c}	0.753
ICSM18 Fab: huPrP^{c}	0.703
VRQ14 Fab:ovPrP^{c}	0.730

#The shape complementarity statistics were calculated by using program CCP4 Sc (Lawrence & Colman, 1993).



Supplementary Figure S1. Plots of the mean pair wise RMSDs to the human prion structure bound with POM1 for each residue of the native human structure from X-ray (red) and NMR studies (green) .The plots were generated by moving a window of three residues along the sequence and plotting the mean pair-wise RMSD (Å) over the central residue. The shaded area represents the region of huPrP^{c} in interaction with POM1 Fab.

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                                          CDR1                                CDR2
POM1 V_H      QVQLQQSGTELVMPGASVKMSCKASGYTFTDYWMHWVKQRPGQGLEWIGSIDPSDSYTSH 60
ICSM18 V_H    EVQLQQSGPELVKPGSSVKISCKASRNTFTDYNLDWVKQSHGKTLEWIGNVYPNNGVTGY 60
VRQ14 V_H     QIQLVQSGPELKKPGETVKISCKASGYTFTNYGMNLVKQAPGKGFEWMGWINTFTGEPTY 60
              ::** ***.**  ** :**:*****  ***:* :. ***  *: :**:* : .  . . :
                                                  CDR3
POM1 V_H      NEKFKGKATLTVDESSSTAYMQLSSLTSEDSAVYFCSRSGYGYYAMEYWGQGTSVTVSSA 12(
ICSM18 V_H    NQKFRGKATLTVDKSSSTAYMELHSLTSEDSAVYYCALY---YYDVSYWGQGTLVTVSSA 117
VRQ14 V_H     ADDFKGRFVFSLDTSASTAYLQINNLKNEDTATYFFTRG------TDYWGQGTTLTVSSA 114
               :.*:*: .:::* *:****::: .*..**:*.*: :         .****** :*****

                                          CDR1                      CDR2
POM1 V_L      DIVLTQSPAILSVSPGERVSFSCRASQNIG-----TSIHWYQQRTNESPRLIIKYASESI 55
ICSM18 V_L    QIVLTQSPAIMSASPGEKVTMTCSASSSV------SYMHWYQQKSGTSPKRWIYDTSKLA 54
VRQ14 V_L     DVVMSQTPLTLSVTIGQPASISCKSSQSLLDSDGKTYLNWLLQRPGQSPKRLIYLVSRLD 60
              ::*::*:*  :*.: *: .:::* :*..:      : ::*  *:.. **:  *  .*.
                                                  CDR3
POM1 V_L      SGIPSRFSGSGSGTDFTLSINSVESEDIADYYCQQSNTWPYTFGGGTKLEL 106
ICSM18 V_L    SGVPARFSGSGSGTSYSLTISSMEAEDAATYFCHQWRSNPYTFGGGTKLEI 105
VRQ14 V_L     SGVPDRFTGSGSGTDFTLKISRVEAEDLGIYFCWQGSHFPQTFGGGTKLEI 111
              **:* **:******.::*.*. :*:** . *:* *    * *********:
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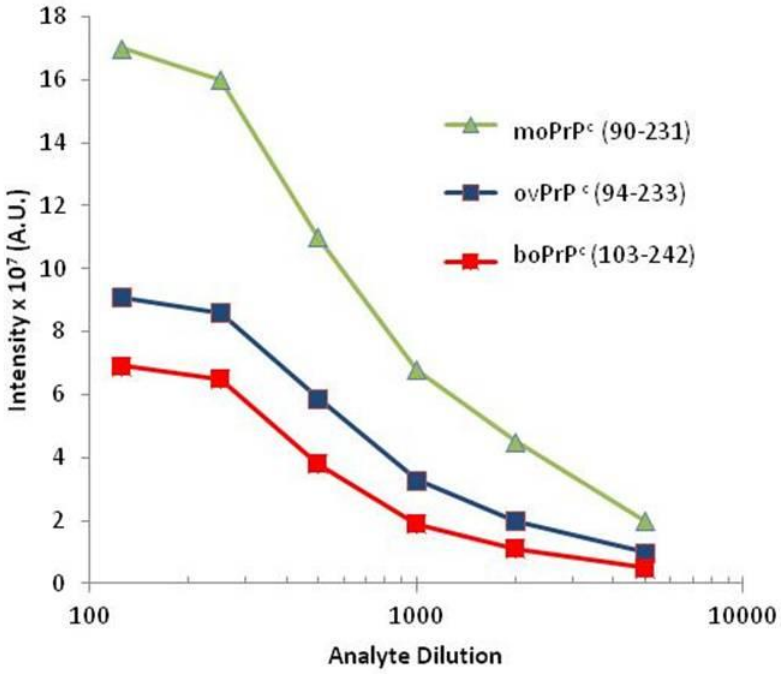
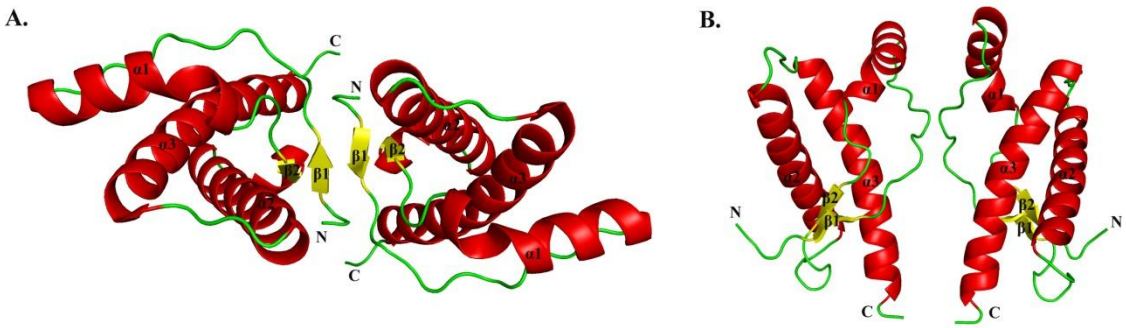
Supplementary Figure S2. Sequence alignment of the variable heavy chains and the variable light chains from POM1 Fab, ICSM18 Fab and VRQ14 Fab.

Supplementary Figure S3. Sequence alignment of the structured C-terminal domain of human, mouse, bovine and sheep prion proteins.



Supplementary Figure S4. ELISA characterization of the binding properties of the Fab fragment antibody POM1 against different prion proteins; moPrP^c, ovPrP^c and boPrP^c are shown in green, blue and red, respectively.



Supplementary Figure S5. The arrangements of the PrP^c chains in the crystal of ICSM18 Fab:$huPrP^c$ and POM1 Fab:$huPrP^c$. (A) Illustration of a 4-stranded antiparallel β sheet structure between the neighboring PrP^c molecules in the crystallographic symmetry related arrangement of ICSM18 Fab:$huPrP^c$. (B) Neighboring PrP^c molecules of the crystallographic symmetry related arrangement of POM1 Fab:$huPrP^c$ interact with one another through the loop structure between sheet β1 and helix α1.