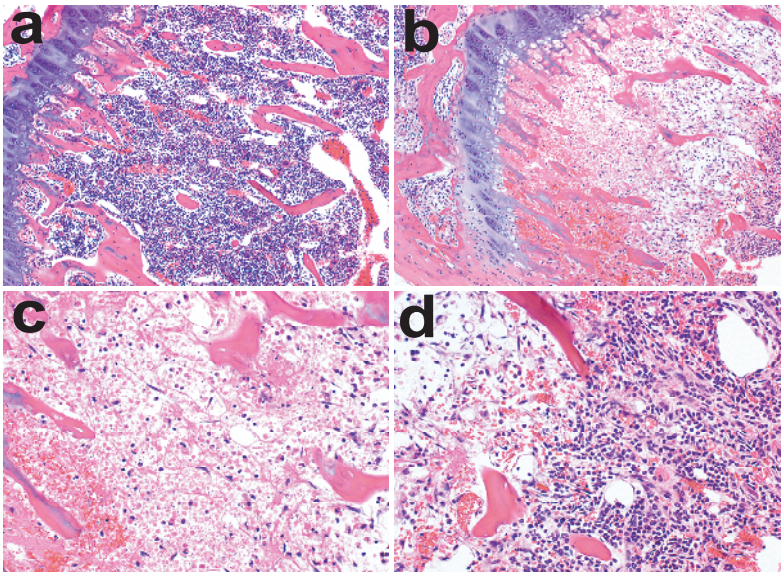

Supplementary Figure 1. Toxicity of the engineered PrAg proteins. Representative microscopic appearance of the bone and bone marrow (femur) at day 7 after treatment of the mice with PBS **(a)** or PrAg-U2-R200A/PrAg-L1-I210A **(b-d)** (45/22.5 µg, in the presence of 3 µg FP59) at day 0, 3, and 6. The bone marrow necrosis was observed in toxin-treated mice (**b**, H&E, 64×) but not in the mock-treated mice (**a**, H&E, 64×). At higher magnification, the necrotic area shows cellular debris and necrotic bone trabeculae (**c**); fibroblastic and vascular proliferations are seen in the periphery of damaged area representing ongoing repair processes (**d**).

Supplementary Table 1. Properties and maximum tolerated doses of the PrAg proteins when injected intraperitoneally at days 0, 3, and 6

PrAg proteins or their combination	Proteolytic cleavage	Group L mutation Subsite II	Group R mutation		MTD3 (μg) FP59=3 μg
			Subsite I	Subsite III	
PrAg	Furin				0.25
PrAg-R200A	Furin	R200A			ND
PrAg-I210A	Furin			I210A	ND
PrAg-L1	MMP				4
PrAg-L1-R178A	MMP		R178A		ND
PrAg-L1-I210A	MMP			I210A	50
PrAg-L1-K214A	MMP			K214A	$\geq$ 50
PrAg-U2	uPA				10
PrAg-U2-K197A	uPA	K197A			ND
PrAg-U2-R200A	uPA	R200A			$\geq$ 100
PrAg-U2-R200A PrAg-L1-I210A	uPA MMP	R200A		 I210A	30 15
PrAg-U2-R200A PrAg-L1-K214A	uPA MMP	R200A		 K214A	30 15

ND: not done. PrAg-L1: previously characterized MMP-activated PrAg protein with furin site RKKR changed to MMP cleavage sequence GPLGMLSQ. PrAg-U2: previously characterized uPA-activated PrAg protein with furin site RKKR changed to uPA cleavage sequence PGSGRSA.