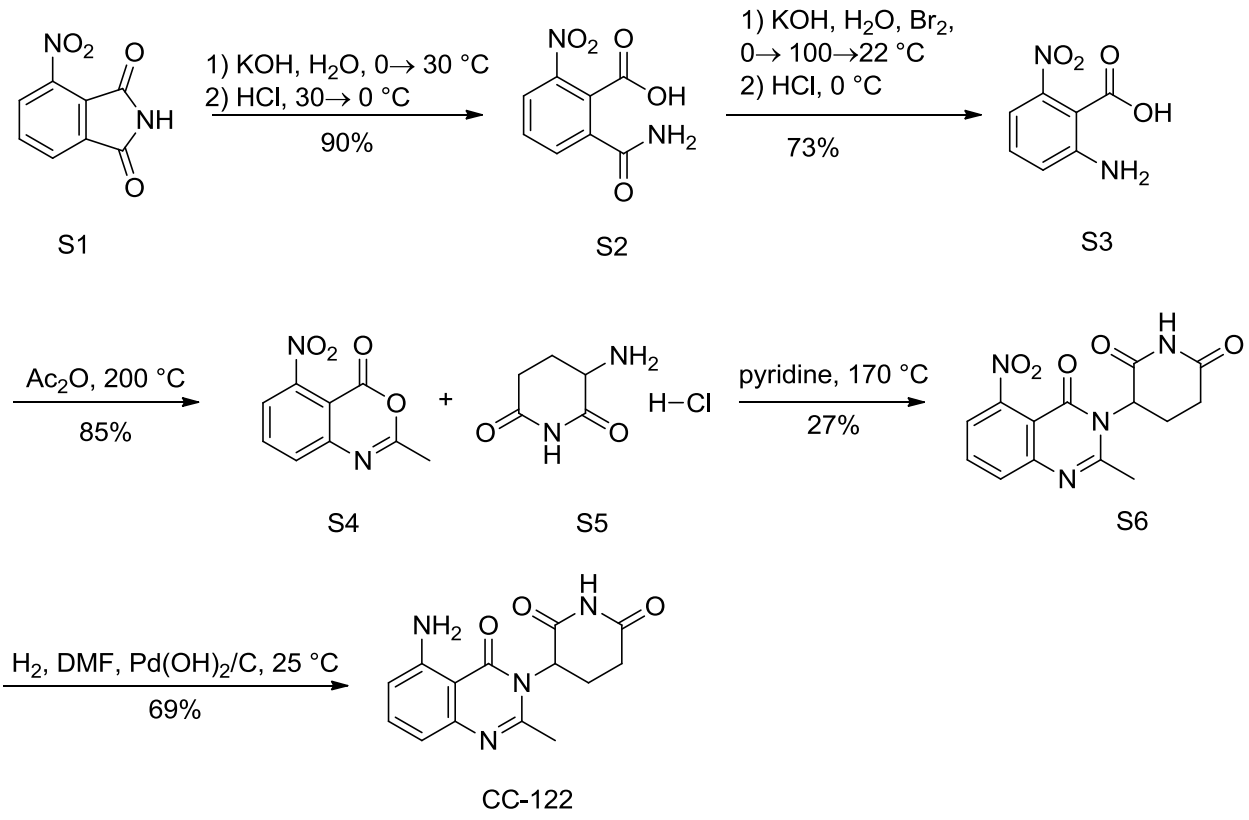
Supplementary Methods:

Scheme S1. Synthesis of CC-122



Step 1: To a solution of potassium hydroxide (16.1 g, 286 mmol) in water (500 mL), was added 4-nitro-1H-isoindole-1,3(2H)-dione (**S1**) (25.0 g, 130 mmol) in portion at 0 °C. The suspension was stirred at 0 °C for 3h, and then heated to 30 °C for 3h. To the solution was added HCl (100 mL, 6N). The resulted suspension was cooled to 0 °C for 1h. The suspension was filtered and washed with cold water (2 x 10 mL) to give 2-carbamoyl-6-nitrobenzoic acid (**S2**) as a white solid (24.6 g, 90% yield): ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.69 (brs, 1H), 7.74 (t, *J* = 8 Hz, 1H), 7.92 (dd, *J* = 1, 8 Hz, 1H), 8.13 (dd, *J* = 1, 8 Hz, 1H), 8.15 (brs, 1H), 13.59 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 125.33, 129.15, 130.25, 132.54, 136.72, 147.03, 165.90, 167.31.

Step 2: To a mixture of 2-carbamoyl-6-nitrobenzoic acid (**S2**) (24.6 g, 117 mmol) and potassium hydroxide (6.56 g, 117 mmol) in water (118 mL) was added a mixture of bromine (6 mL),

potassium hydroxide (13.2 g, 234 mmol) in water (240 mL) at 0 °C, and followed by addition of a solution of potassium hydroxide (19.8 g, 351 mmol) in water (350 mL). After 5 min at 0 °C, the mixture was transferred to a 100 °C oil bath and kept for 1h. The solution was cooled to room temperature than in an ice-water bath for 30 min. To the mixture was added a solution of HCl (240 mL, 2N) dropwise at 0 °C, and kept for 1h. The suspension was filtered and washed with water (5 mL) to give 2-amino-6-nitro-benzoic acid (**S3**) as yellow solid (15.6 g, 73% yield): HPLC: Waters Symmetry C_{18}, 5µm, 3.9 x 150 mm, 1 mL/min, 240 nm, CH_3CN/0.1% H_3PO_4, 5% grad to 95% over 5 min, 5.83 min (85%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.90 (dd, *J* = 1, 8 Hz, 1H), 7.01 (dd, *J* = 1, 9 Hz, 1H), 7.31 (t, *J* = 8 Hz, 1H), 8.5-9.5 (brs, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 105.58, 110.14, 120.07, 131.74, 149.80, 151.36, 166.30; LCMS: MH = 183.

Step 3: A mixture of 2-amino-6-nitro-benzoic acid (**S3**) (1.5 g, 8.2 mmol) in acetic anhydride (15 mL) was heated at 200 °C for 30 min in a microwave oven. The mixture was filtered and washed with ethyl acetate (20 mL). The filtrate was concentrated in vacuo. The solid was stirred in diethyl ether (20 mL) for 2h. The suspension was filtered and washed with diethyl ether (20 mL) to give 2-methyl-5-nitro-4H-3,1-benzoxazin-4-one (**S4**) as a light brown solid (1.4 g, 85% yield): HPLC: Waters Symmetry C_{18}, 5µm, 3.9 x 150 mm, 1 mL/min, 240 nm, CH_3CN/0.1% H_3PO_4, 5% grad 95% in 5 min, 5.36 min (92%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.42 (s, 3H), 7.79 (dd, *J* = 1, 8 Hz, 1H), 7.93 (dd, *J* = 1, 8 Hz, 1H), 8.06 (t, *J* = 8 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.87, 107.79, 121.54, 128.87, 137.19, 147.12, 148.46, 155.18, 161.78; LCMS: MH = 207.

Step 4: Two vials each with a suspension of 2-methyl-5-nitro-4H-3,1-benzoxazin-4-one (**S4**) (0.60 g, 2.91 mmol) and 3-amino-piperidine-2,6-dione hydrogen chloride (**S5,** Suven Life Sciences) (0.48 g, 2.91 mmol) in pyridine (15 mL) were heated at 170 °C for 10 min in a microwave oven. The suspension was filtered and washed with pyridine (5 mL). The filtrate was combined and concentrated in vacuo. The resulted mixture was stirred in HCl (30 mL, 1N), ethyl acetate (15 mL) and diethyl ether (15 mL) for 2h. The suspension was filtered and washed with water (30 mL) and ethyl acetate (30 mL) to give a dark brown solid, which was stirred with methanol (50 mL) at room temperature overnight. The suspension was filtered and washed with methanol to give 3-(2-methyl-5-nitro-4-oxoquinazolin-3(4H)-yl)piperidine-2,6-dione (**S6**) as a

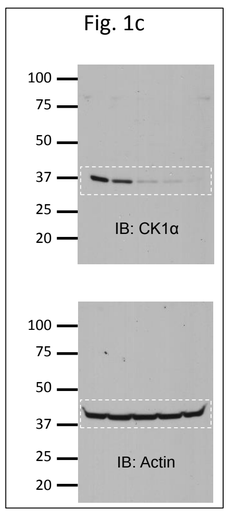
black solid (490 mg, 27% yield). The solid was used in the next step without further purification.

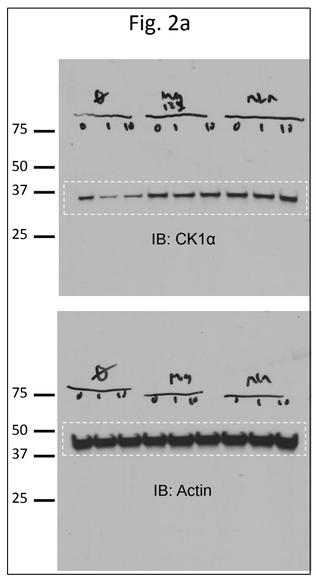
Step 5: A mixture of 3-(2-methyl-5-nitro-4-oxoquinazolin-3(4*H*)-yl)piperidine-2,6-dione (**S6**) (250 mg) and $Pd(OH)_2$ on carbon (110 mg) in DMF (40 mL) was shaken under hydrogen (50 psi) at room temperature for 12h. The suspension was filtered thru a pad of Celite and washed with DMF (10 mL). The filtrate was concentrated and the resulted oil was purified with column chromatography (Silica Gel, methanol/methylene chloride) to give 3-(5-amino-2-methyl-4-oxoquinazolin-3(4*H*)-yl)piperidine-2,6-dione as a white solid (**CC-122**) (156 mg, 69% yield); HPLC: Waters Symmetry C_{18}, 5μm, 3.9 x 150 mm, 1 mL/min, 240 nm, 10/90 CH_3CN/0.1% H_3PO_4, 3.52 min (99.9%); mp: 293-295 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.10-2.17 (m, 1H), 2.53 (s, 3H), 2.59-2.69 (m, 2H), 2.76-2.89 (m, 1H), 5.14 (dd, *J* = 6, 11 Hz, 1H), 6.56 (d, *J* = 8 Hz, 1H), 6.59 (d, *J* = 8 Hz, 1H), 7.02 (s, 2H), 7.36 (t, *J* = 8 Hz, 1H), 10.98 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.98, 23.14, 30.52, 55.92, 104.15, 110.48, 111.37, 134.92, 148.17, 150.55, 153.62, 162.59, 169.65, 172.57; LCMS: MH = 287; [M+1]+ calcd for $C_{14}H_{14}N_4O_3$, 287.1144. found, 287.1148; analysis (% calcd, % found for $C_{14}H_{14}N_4O_3$ + 0.3 H_2O): C (57.65, 57.50), H (5.05, 4.73), N (19.21, 19.00).

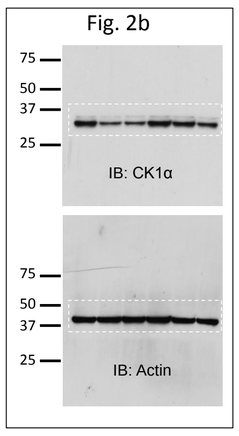
Supplementary Note:

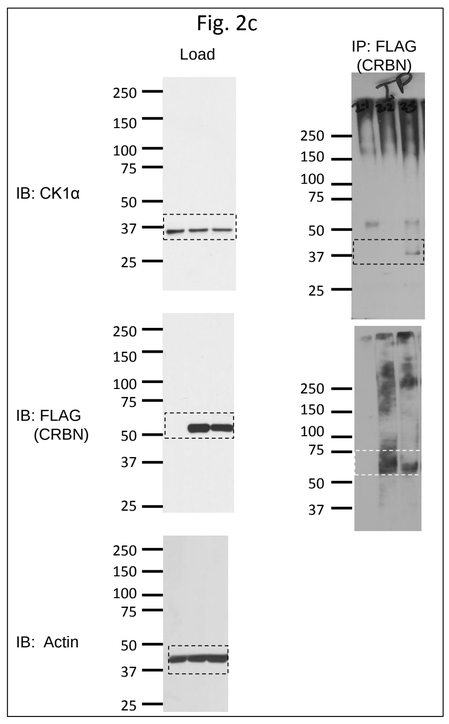
Pharmacokinetics of lenalidomide in humans

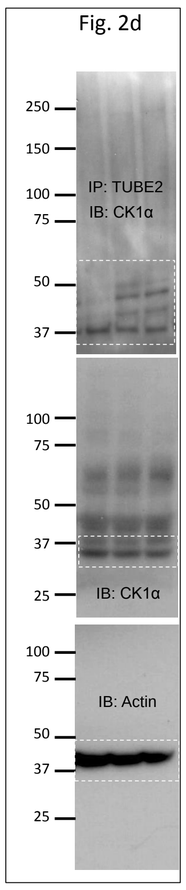
The standard dose of lenalidomide in del(5q) MDS patients is 10 mg once daily. The Cmax in these patients is 222 ng/ml, corresponding to 856 nM, with a half-life of 3.2 to 3.8 hours (Assessment Report of the European Medicine Agency, 2013). Based on these numbers a concentration of >100 nM is maintained for at least 10 hours. In KG-1 cells, 10 nM lenalidomide decreased CK1α protein levels, and near maximal activity was seen at 100 nM (Figure 1C), implying that the lenalidomide concentrations achieved in patients are sufficient for degradation of CK1α.

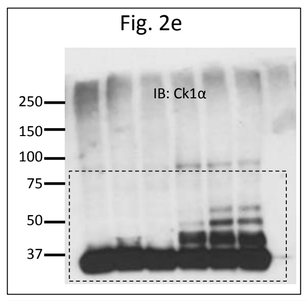


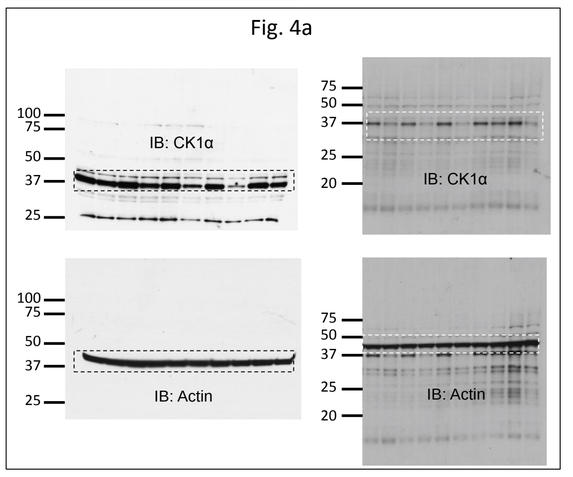


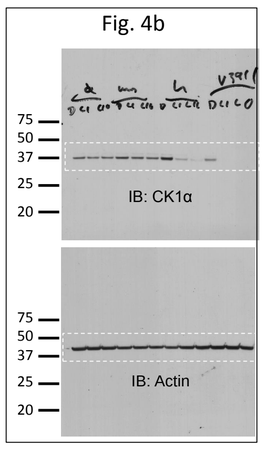


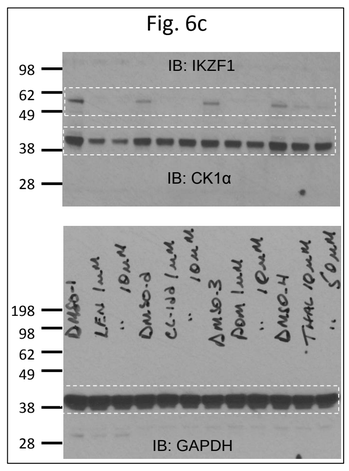


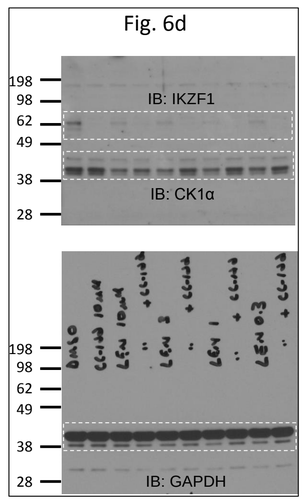


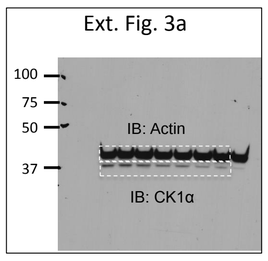


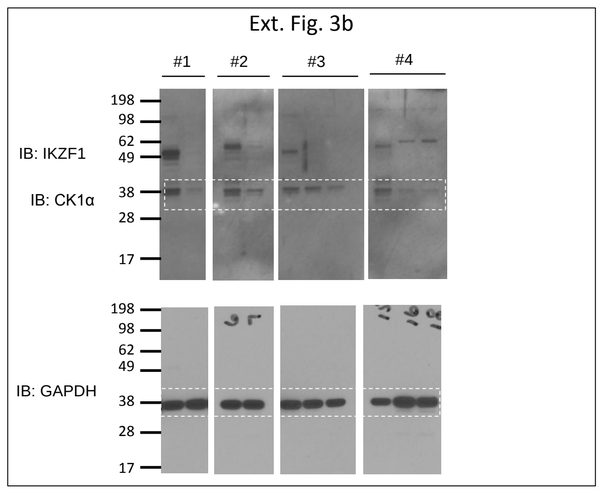


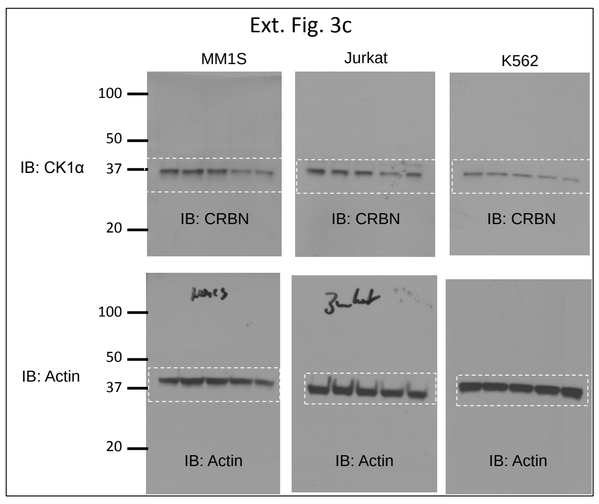


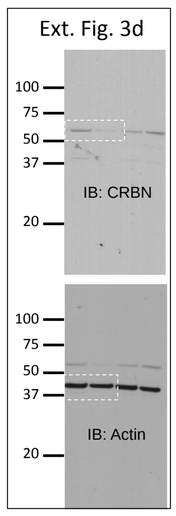


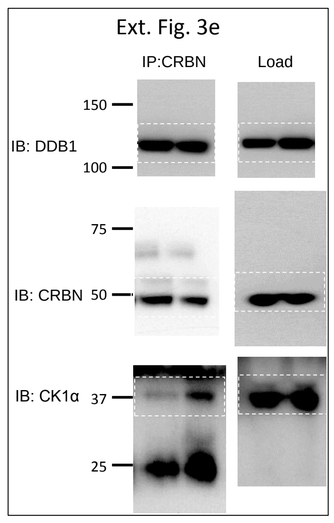


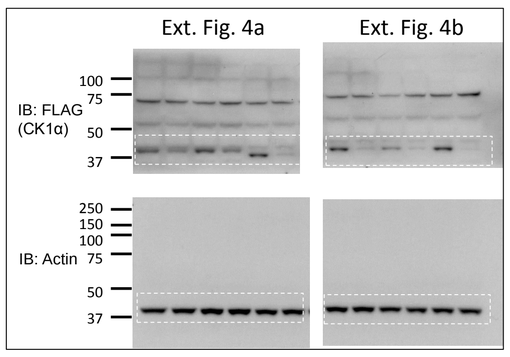


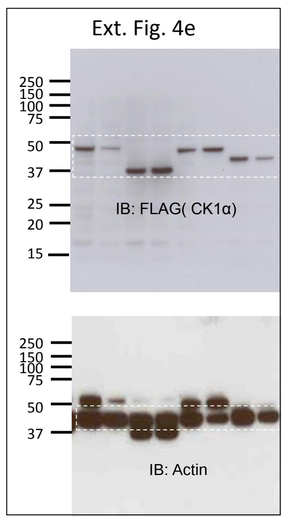


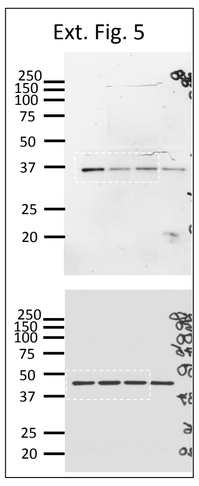


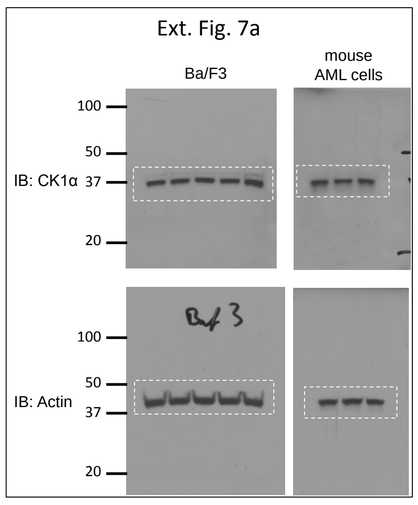


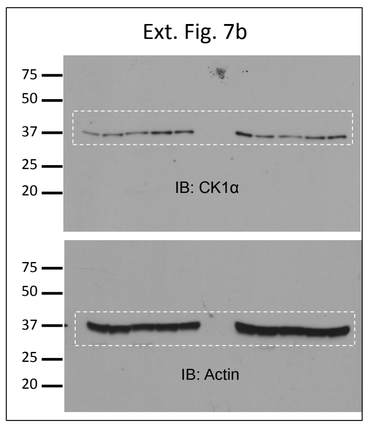


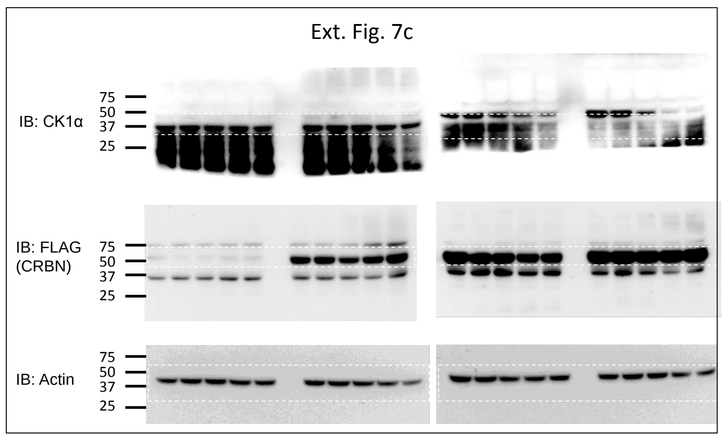


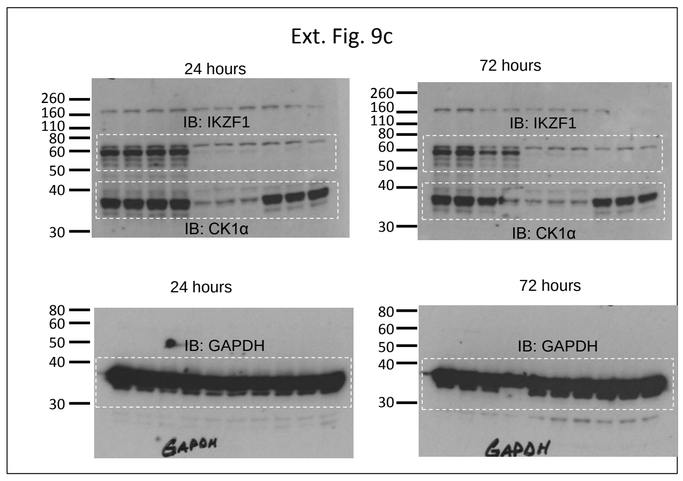


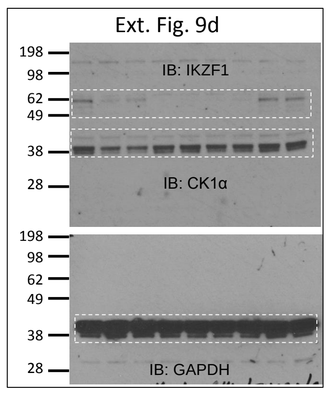


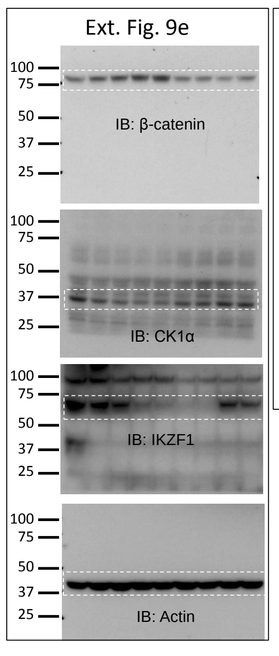


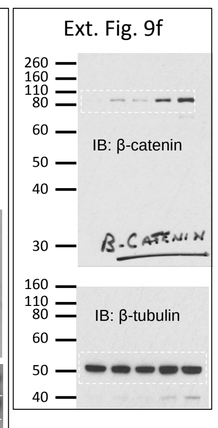


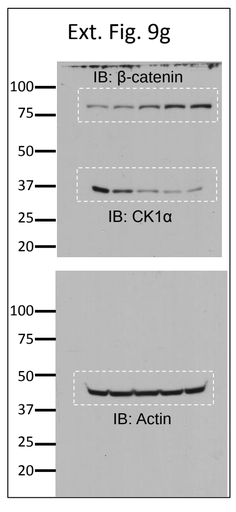












Supplementary Figure 1: Full uncropped scans of all Western Blots with molecular weight markers