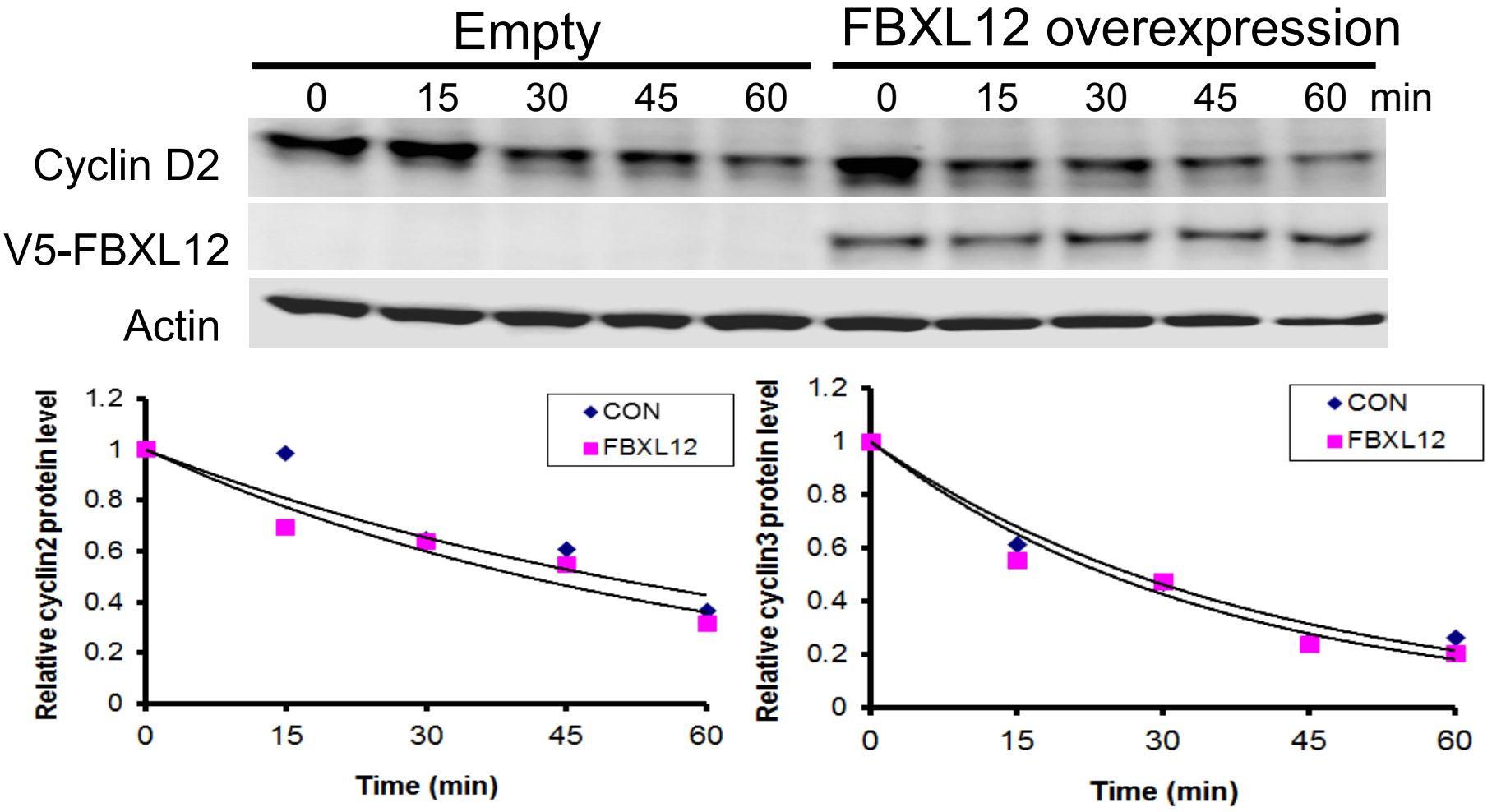
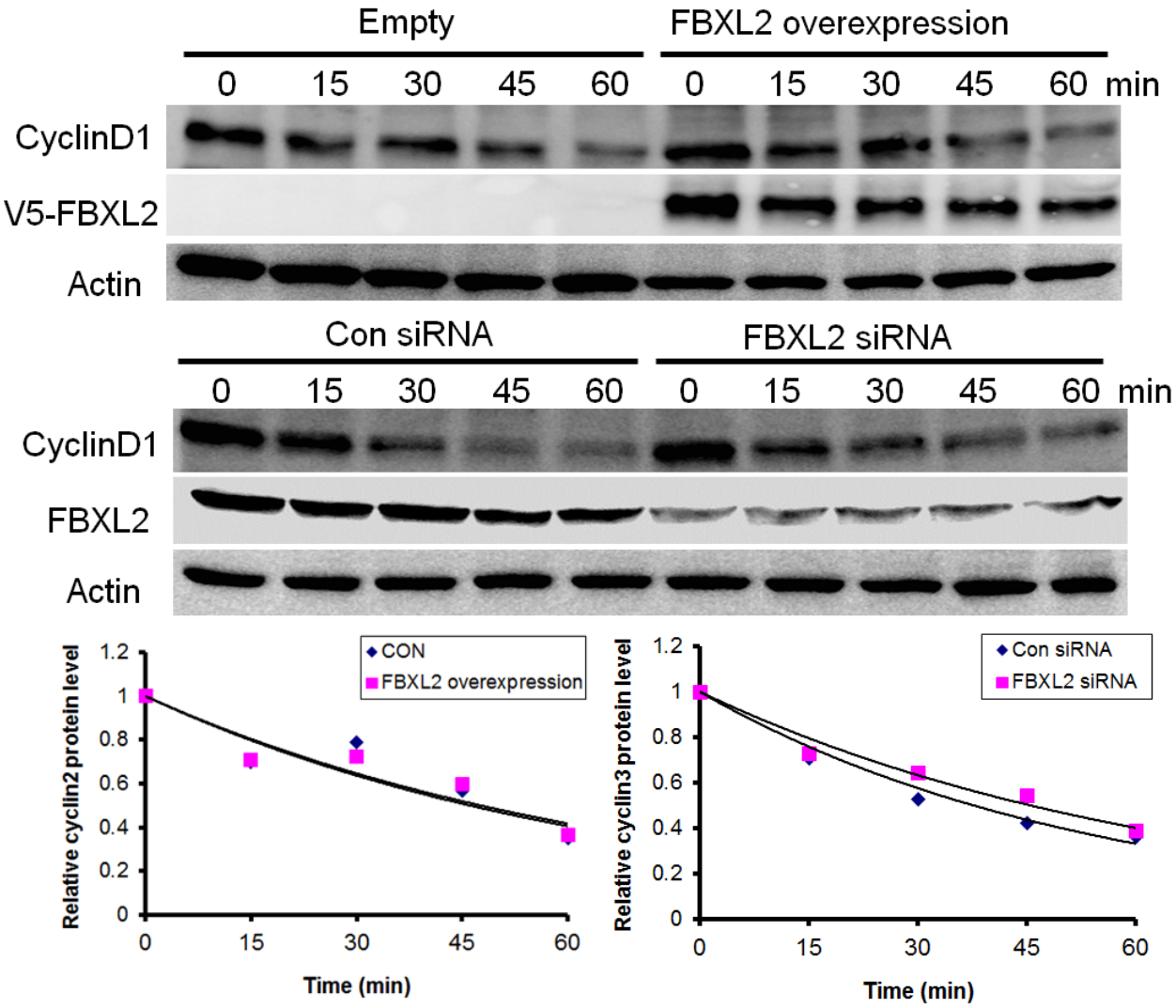
Table 1

Sample #	Age	Sex	Year	Diagnosis	Background
1	34	Female	2008	ALL	History: The patient's medical history includes obesity, hyperlipidemia, and arthritis. At the time of testing she presented with thrombocytopenia, circulating blasts, and an elevated white blood cell count.
					Diagnostics: Flow cytometric analysis on peripheral blood displayed an immunophenotype ewith positive CD10, HLA-DR, CD19, TdT, CD34, CD20 (dim), CD22 (dim, and CD33 (dim) and negative CD5 (85%) and surface immunoglobulin in B-lineage lymphoblasts. Also identified were a small percentage of heterogeneous T-cells and mature B-cells.
2	37	Male	2009	ALL	History: The patient was diagnosed with Philadelphia chromosome positive precursor-B cell acute lymphoblastic leukemia. At the time of testing the patient had relapsed and was receiving chemotherapy.
					Diagnostics: Flow cytometric analysis on peripheral blood displayed a population of abnormal precursor B-cells (36.4%) and an immunophenotype with positive CD38 (dim), CD19, CD22, CD20 (partial), CD10, CD34, CD13/33 (dim) and TdT, and negative cCD3 and MPO.
3	68	Male	2009	AML	History: The patient's medical history includes hypothyroidism and prostate carcinoma, status post prostatectomy. At the time of testing the patient presented with blasts in the peripheral blood and pancytopenia.
					Diagnostics: Flow cytometric analysis on peripheral blood displayed a population of myeloblasts (89%) with an immunophenotype with positive CD45, CD117, CD33 and MPO, and negative CD34, HLA-DR, CD14, and CD15. Also seen were a few B-cells, granulocytes, and T-cells.
4	70	Male	2009	AML	History: The patient had a medical history of colon cancer and he received neoadjuvant chemotherapy. At the time of testing the patient presented with blasts in the peripheral blood and leukocytosis.
					Diagnostics: Flow cytometric analysis on peripheral blood displayed a population of blasts (56%) with an immunophenotype exhibiting positive CD34, CD33, CD13, HLA-DR, CD45 (dim), CD38 (partial), CD22 (partial) and CD4 (partial), and negative CD14, CD64, CD36, CD7, MPO and TdT. There were also a few granulocytes (displaying possible hypergranularity), monocytes with weak CD33 staining, very little heterogeneous T-cells and a few B-cells.
5	67	Female	2009	AML	History: The patient had a medical history of esophageal reflux, obesity, dyslipidemia, hypertension, and recently leukocytosis and diverticulitis. At the time of testing the patient presented with deep vein thrombosis, bilateral pulmonary emboli, leukocytosis, thrombocytopenia, and anemia.
					Diagnostics: Flow cytometric analysis on peripheral blood displayed a population of abnormal blast/leukemic cells (86%) and an immunophenotype with positive CD45 (dim), CD33, CD117 (very dim), CD56 (subset), CD13 (very weak) and MPO, and negative CD2, CD3, CD4, CD10, CD14, CD19, CD20, CD22, CD 34, CD36, CD64m HLA-DR, CD11b, TdT, and cCD3.
6	52	Female	2009	ALL	History: The patient had a medical history including anemia, thrombocytopenia, leukocytosis, and blasts in her peripheral blood.
					Diagnostics: Flow cytometric analysis on peripheral blood displayed a population of B-lymphoblasts (68%) with an immunophenotype exhibiting positive CD45 (dim), CD19, CD34, CD10, CD22 (partial), CD33 (partial), CD38, HLA-DR, CD13 and TdT, and negative surface immunoglobulin, CD20, and CD117. Also identified were T-cells, few B-cells, granulocytes, and few monocytoid cells.
7	59	Female	2009	AML	History: The patient had a medical history including hypothyroidism and was status post cholecystectomy. At the time of testing the patient presented with anemia, thrombocytopenia, leukocytosis and shortness of breath.
					Diagnostics: Bone marrow aspirate was taken and flow cytometric analysis displayed an increased abnormal population of myeloblasts. The immunophenotype exhibited positive CD45 (dim), CD117, CD33, CD13, CD4, CD64 (partial), HLA-DR, CD15 (partial) and MPO (partial), and negative CD34, CD36, CD14, CD10, and TdT. The monocytic population was increasingly positive for CD14, CD45, and coexpressed CD36 and CD64. CD13/33 positive myeloid cells also expressed CD56.
8	38	Female	2010	AML	History: The patient's medical history included asthma, diverticulosis, endometriosis, status post hysterectomy, GERD, gastric polyp, hypothyroidism, obesity and migraines. At the time of testing the patient presented with leukocytosis and shortness of breath.
					Diagnostics: Flow cytometric analysis on peripheral blood displayed a population of myeloid cells (80%) which had a immunophenotype exhibiting positive CD45 (weak), CD13, CD15, CD33, CD4, CD6, CD14, CD11b, CD16, CD56 (weakly coexpressed), MPO and HLA-DR, with coexpression of CD 36, and negative for CD34, CD117, and TdT with no evidence of coexpression with CD19, CD22, CD7 and CD3. Other cells identified include T-cells, phenotypic natural killer cells, polytypic B-cells, B-cells, and few mature granulocytes.
9	63	Male	2010	ALL	History: The patient had a medical history including renal insufficiency and hypothyroidism. At the time of testing the patient presented with anemia, leukocytosis, and thrombocytopenia.
					Diagnostics: Bone marrow was taken and flow cytometric analysis displayed an increase in phenotypic lymphoblasts (92%) with a immunophenotype positive for CD45 (dim), CD19, CD38 (partial), CD22 (weak), CD34 (coexpressed in 9%), HLA-DR and TdT, and negative for CD10, CD20, CD13, CD33, CD117, CD14, CD36, CD64, CD3, CD7, MPO, and surface immunoglobulin light chains. Small amounts of heterogeneous T-cells, phenotypic natural killer cells, polytypic surface positive immunoglobulin positive mature B-cells, myeloid cells, granulocytic cells, and monocytic cells were also identified.
10	38	Female	2010	ALL	History: The patient's medical history included breast cancer status post chemotherapy and B-lymphoblastic leukemia. At the time of testing she presented with leukocytosis ad headache. The patient had received chemotherapy 3 weeks prior to testing.
					Diagnostics: Flow cytometric analysis on peripheral blood displayed a blast population (79%) with a immunophenotype positive for CD45 (dim), CD34, TdT (partial), CD19, CD22 (partial), HLA-DR, CD38, and CD15 (weak), and negative for CD20, CD10, surface immunoglobulin, CD13, and CD33. Also identified were granulocytes and few polytypic B-cells.

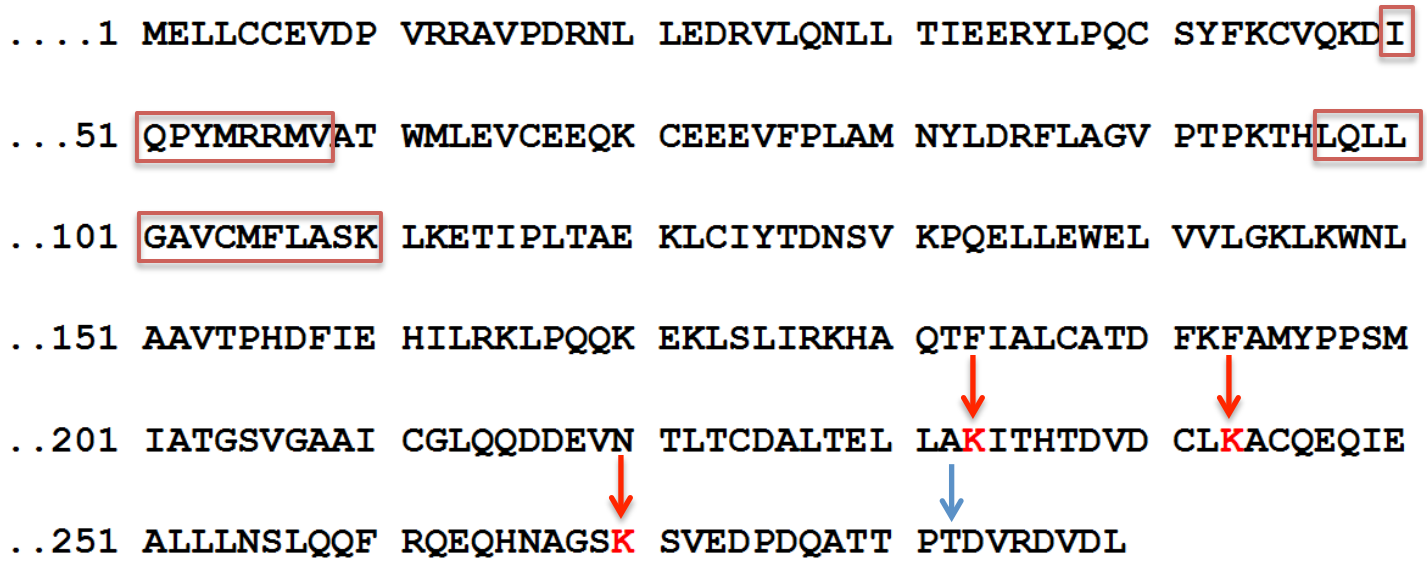
*Abbreviations: HLA=human leukocyte antigen, TdT= terminal deoxynucleotidyl transferase, MPO= myeloperoxidase, GERD= gastroesophageal reflux disease **Percentages represent amount from total cell number.



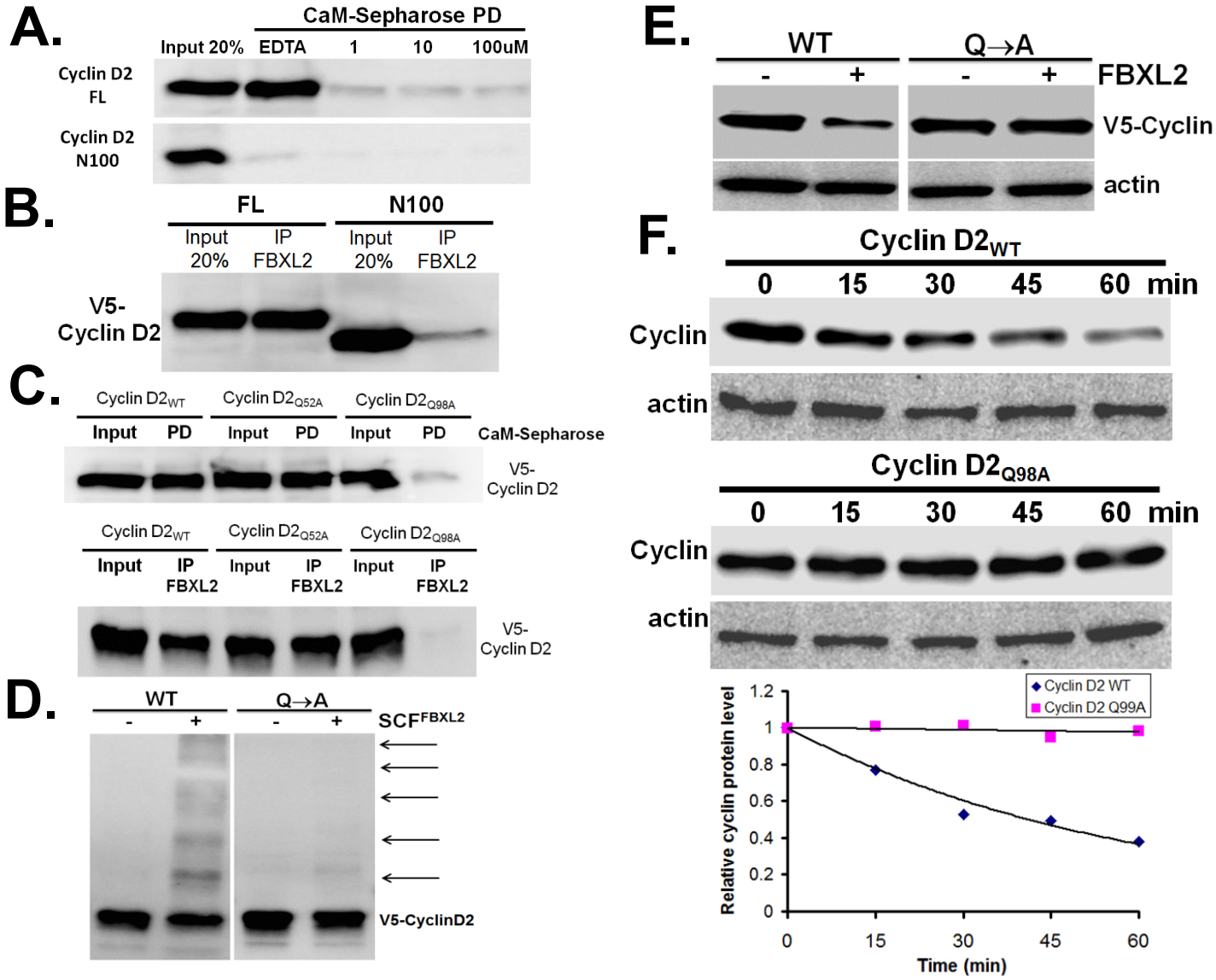
Supplementary Figure 1. FBXL12 overexpression does not change half-life of cyclin D2. MLE cells were transfected with either empty plasmid or FBXL12 plasmid. 24 h later, cells were exposed to 40ug/ml of cycloheximide at different time points. Cells were collected, equal amounts of protein were resolved on SDS-PAGE followed by cyclin D2, V5-FBXL2 and actin immunoblotting. Endogenous cyclin D2 protein levels were quantitated by image J software. The levels of cyclin D2 are expressed as the percent of the initial levels present at time zero. The data represents n=2 experiments.



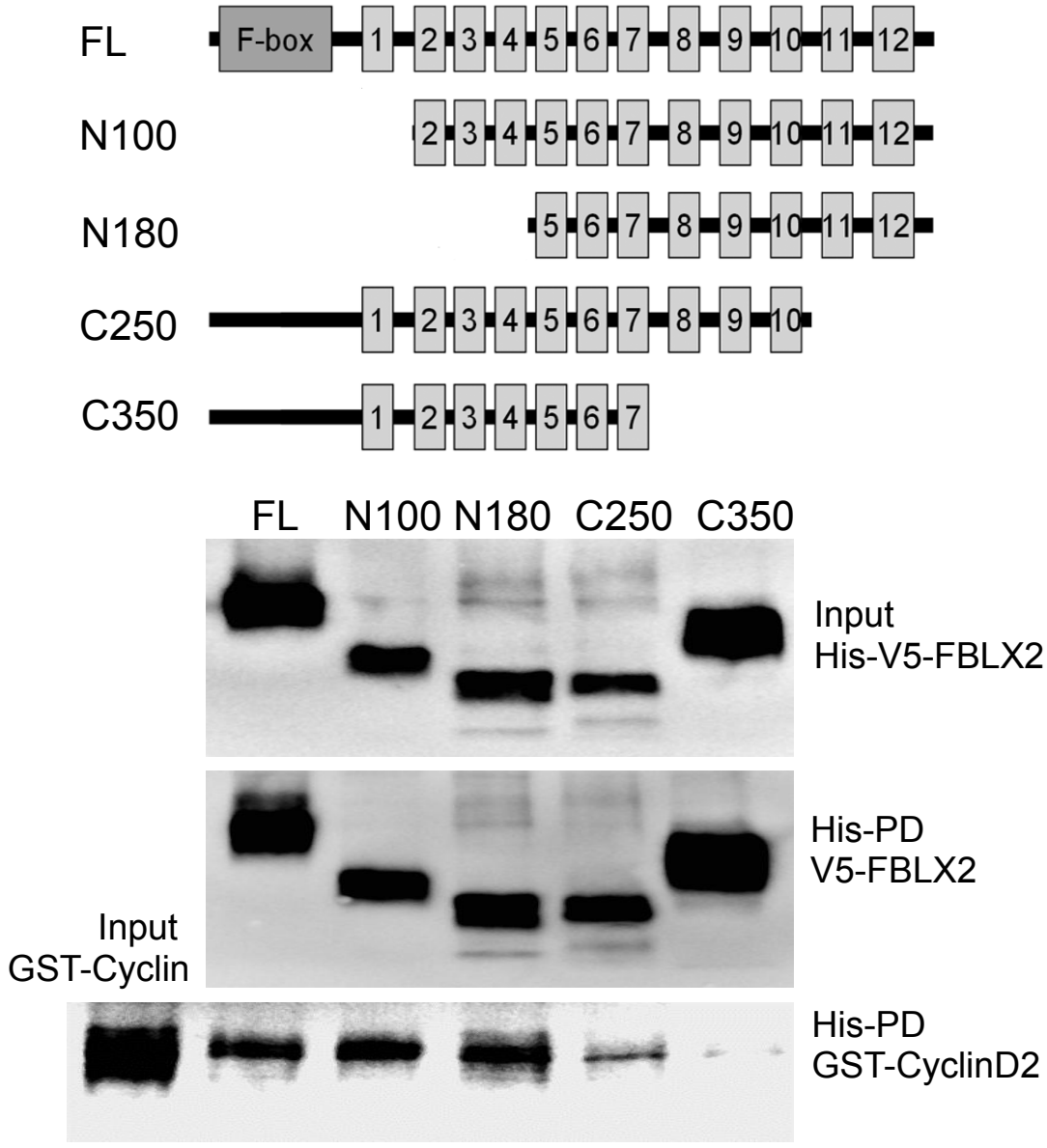
Supplementary Figure 2. FBXL2 overexpression and knockdown does not change half-life of cyclin D1. MLE cells were transfected with either empty plasmid or FBXL2 plasmid, or control RNA (Con) or FBXL2 siRNA. 24 or 48 h later, cells were exposed to 40ug/ml of cycloheximide at different time points. Cells were collected, equal proteins were resolved on SDS-PAGE followed by cyclin D1, V5-FBXL2 and actin immunoblotting. Endogenous cyclin D1 protein levels were quantitated by imageJ software. The levels of cyclin D1 are expressed as the percent of the initial levels present at time zero. The data represents n=2 experiments.



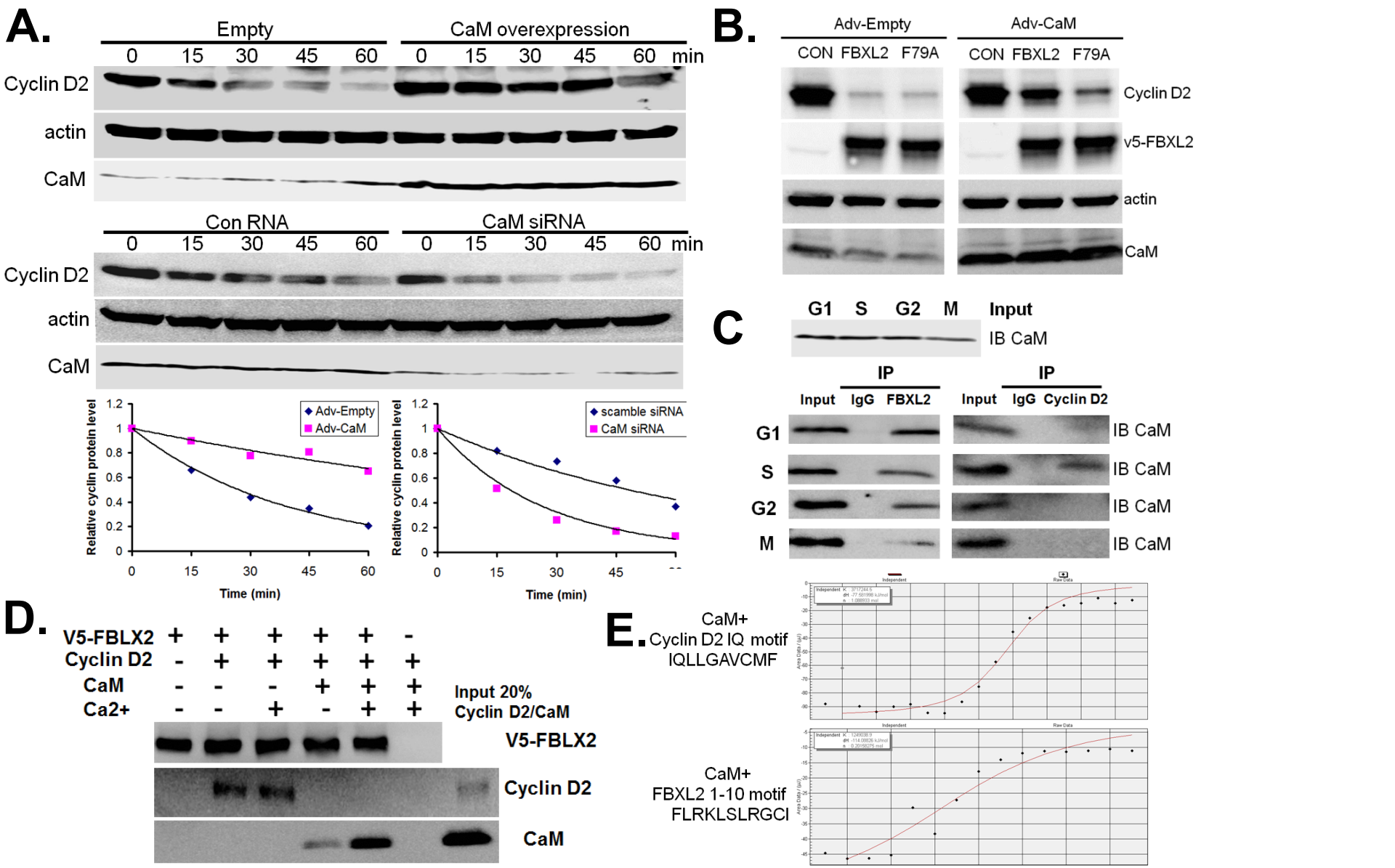
Supplementary Figure 3. Sequence of cyclin D2. Red rectangle represents a potential IQ motif within cyclin D2 . Red arrows indicate potential ubiquitination sites within cyclin D2. Blue arrow indicates a potential phosphorylation site within cyclin D2.



Supplemental Figure 4. **FBXL2 and CaM both vie for cyclin D2 docking.** **A.** CaM-sepharose pull-down assays showing effects of exogenous calcium on binding between CaM and either V5-full-length (FL) cyclin (upper panel) or a V5-NH_2-terminal truncated (N100) mutant lacking the IQ motif within cyclin D2 (lower panel). **B.** Co-immunoprecipitation of endogenous FBXL2 and V5-immunoblotting for FL or NH_2-terminal truncated (N100) mutant cyclin D2 after cellular expression of these cyclins. **C.** CaM-sepharose pull-down assays showing levels of binding between CaM and WT cyclin D2 or D2 variants harboring point mutations within IQ motifs (upper panel). Cells were transfected with V5-cyclin D2 variants harboring point mutations within IQ motifs followed by co-immunoprecipitation of endogenous FBXL2 and V5-immunoblotting (lower panel). **D.** *In vitro* ubiquitination assays. Purified SCF complex were incubated with WT V5-cyclin D2, or an IQ motif point mutant, and the full complement of ubiquitination reaction components. **E.** Cells were co-transfected with WT cyclin D2 or a variant harboring a point mutation within the IQ motif with or without FBXL2 plasmid followed by immunoblotting for cyclin D2. **F.** Cyclin D2 protein half-life determination after expression of WT V5-cyclin D2, or an IQ motif point mutant (*n=2* experiments). Below levels of each protein on immunoblots was quantified densitometrically and is shown graphically.



Supplementary Figure 5. Cyclin D2 interacts with FBXL2. A. Map of FBXL2 mutants. **B**. Cell lysate containing FBXL2 truncation mutants shown in (A) or co-purified with GST-cyclin D2 through his pull-down (His-PD). After washing, proteins were eluted and processed for V5 or cyclin D2 immunoblotting.



Supplemental Figure 6. **Calmodulin is an FBXL2 antagonist.** **A.** Cyclin D2 protein half-life determination after CaM overexpression, or CaM knockdown using siRNA (*n=2* experiments). Below each panel levels of each protein on immunoblots was quantified densitometrically and is shown graphically. **B.** Levels of endogenous cyclin D2 protein in cells after co-expression of either Adv-empty, Adv-CaM, or WT FBXL2 or a FBXL2 mutant (F79A) that lacks ability to bind CaM. **C.** MLE cells were synchronized to each cell phase, followed by co-immunoprecipitation of endogenous FBXL2, cyclin D2, and immunoblotting for CaM. Top immunoblot: input of CaM in total cell lysates prior to i.p. **D.** V5-FBXL2-agarose beads were generated and used as bait and incubated with combinations of purified GST-cyclin D2, or CaM with or without exogenous calcium. After washing of beads (150mM NaCl, 0.1% Triton X-100), proteins were eluted and resolved by SDS-PAGE followed by cyclin D2, CaM, and V5 immunoblotting. **E.** ITC binding analysis of CaM and peptide (LQLLGTVCLL) encoding a CaM-binding motif within cyclin D2 and peptide (79FLRKLSLRGCI89) encoding a CaM-binding motif within FBXL2 *in vitro*.