Supplemental Figures 1-19

Figure S1: FACS analyses of CXCR4 silenced in Jeko, SP53 and Z138 MCL cells. GFP-positive cells were sorted after infection and CXCR4 expression was evaluated using FACS analyses. 94-74% reduction was noted in all knock down cells.

Figure S2: Migration of MCL cells to SDF-1 was effectively decreased after CXCR4 silencing. GFP-positive controls or CXCR4 silenced MCL cells (10^5) were placed in upper chambers with different concentrations of SDF-1 in lower chambers and the cells were counted in the lower chamber after 24 hours.

Figure S3: CXCR4 silenced cells showed reduction of migration toward the medium harvested from HS27a culture. Medium from HS27a was harvested after 3 days and 600 μL was added to transwell. GFP-positive controls or CXCR4 silenced MCL cells (Jeko, SP53, Z138 and REC1, 10^5) were placed in upper chambers with HS27a medium in lower chambers and cells were counted in the lower chambers after 24 hours.

Figure S4: SDF-1 protects the MCL cells from starvation induced cell death but neutralized antibodies were reversed the effect of protection. MCL cells ($1x10^6$) were cultured in low serum for three days and SDF-1 (10ng/ml) or neutralizing SDF-1 antibodies were added to the culture. Cell death were evaluated based on 7-AAD/Annexin V staining using FACS.

Figure S5: Colonies from PHA-LCM medium was harvested and light chain restriction was analyzed using fix and perm cell permeabilization kit (Invitrogen). Colonies harvested from PHA-LCM medium were lambda restricted similar to the SP53 parent cells.

Figure S6: CXCR4 silencing decreases the motility of MCL cells. We quantitatively measured the distances the CXCR4-silenced or control cells travelled over 2 days using a time-lapse microscopy. Distances (mm) traveled by CXCR4-silenced SP53 and REC1 cells, which were an average of results from 15 different wells, were significantly decreased compared to the control cells.

Figure S7: Bortezomib IC50 was calculated using different MCL cells. IC_{50} value (the concentration of a drug that is required for 50% inhibition *in vitro*) was used to indicate the quantitative measure of the different cell killing effect of drugs. The Hill-Slope logistic model is used to calculate IC_{50} using MS Excel.

Figure S8A&B: **(A)** HS27a stromal cells as well as HS27a media protect MCL cells from chemotherapeutic drug cytotoxicity. CD19+ cells were isolated from four different patient cells (10^5) and were cultured with HS27a stromal cells or 1 ml of 1:1 diluted HS27a medium. Cell viability was determined by the CellTiter-Blue® fluorometric assay (Promega) and was indicated as a ratio compared to cell viability without treatment. Bortezomib was serially diluted (0-40 nM) as indicated. The results represent the mean ± standard deviation of triplicates. *, $P<0.05$; **, $P<0.005$. *P* values were calculated using Student's *t*-test.
(B) AMD3100 treatment abolishes the protective effects of the stromal cells against chemotherapeutic drugs. A CXCR4 antagonist, AMD3100 (40 mM), was incubated with MCL cells for 24 hours, and cell viability was determined by CellTiter-Blue. The results represent the mean ± standard deviation of triplicates. *, $P<0.05$, **, $P<0.005$; *P* values were calculated using Student's *t*-test.

Figure S9: Bortezomib treatment induces CXCR4 expression in MCL cells. Bortezomib-resistant Mino and REC1 cells (10^6, 6-well plate) were treated with different doses of bortezomib (0-100 nM for 24 hours). CXCR4 expression was analyzed by FACS.

Figure S10: ROS generated after bortezomib treatment induces CXCR4 upregulation in MCL cells. Bortezomib-resistant Mino and REC1 cells (10^6, 6-well plate) were treated with bortezomib (30 nM for 24 hours) with or without NAC (100 mM, 1 hour).
CXCR4 expression was evaluated using FACS.

Figure S11: Ibrutinib IC50 was calculated using different MCL cells. IC_{50} value (the concentration of a drug that is required for 50% inhibition *in vitro*) was used to indicate the quantitative measure of the different cell killing effect of drugs. The Hill-Slope logistic model is used to calculate IC_{50} using MS Excel.

Figure S12: HS27a stromal cells as well as HS27a media protect MCL cells from Ibrutinib cytotoxicity. CD19+ cells were isolated from four different patient cells (10^5) and were cultured with HS27a stromal cells or 1 ml of 1:1 diluted HS27a medium. Cell viability was determined by the CellTiter-Blue® fluorometric assay (Promega) and was indicated as a ratio compared to cell viability without treatment. Ibrutinib was serially diluted (0-40 nM) as indicated. The results represent the mean ± standard deviation of triplicates. *, $P<0.05$; **, $P<0.005$. *P* values were calculated using Student's *t*-test.

Figure S13: ROS weren't generated after Ibrutinib treatment. Jeko and SP53 cells (10^6, 6-well plate) were treated with Ibrutinib (0, 20, 40 μM for 24 hours) and ROS was measured using DCH-FDA (Sigma-Aldrich). ROS was measured at Ex/Em, 480/520 nm and then analyzed by flow cytometry.

Figure S14: Ibrutinib treatment did not induce CXCR4 upregulation in MCL cells. Jeko and SP53 cells (10^6, 6-well plate) were treated with Ibrutinib (0, 20 and 40 μM) and CXCR4 expression was evaluated using FACS.

Figure S15: A model diagram depicting observations made in the study. Ibrutinib treatment does not produce ROS as well as does not induce upregulation of CXCR4.

Figure S16: Bortezomib (30 nM) was added to the MCL cells with or without lysosomal inhibitor chloroquine (50 μM), and autophagy induction was analyzed based on the LC3B-I to LC3B-II conversion as measured by immunoblots.

Figure S17: Beclin1 was knocked down using lentivirus mediated shRNA in Jeko cells and Beclin1 levels were evaluated using immunoblots. GFP+ cells were selected followed by antibiotic selection to ensure knock down. Densitometer analysis showed a significant down-regualtion of beclin 1 in GFP+ Jeko cells compared to GFP+ scrambled shRNA infected Jeko cells.

Figure S18: Jeko cells were cultured in low serum condition with AMD3100 to inhibit CXCR4 expression and autophagy expression was analyzed using immunoblots based on LC3-I to LC3-II conversion.

Figure S19: Beclin 1 silencing does not change CXCR4 expression in MCL cells.