**Supplement**

**Figure legends**

**Supp. Figure 1. Detection of doxorubicin in the exosomes by HPLC and visualization of vesicular transport.** Cell lines SU-DHL-4, OCI-Ly1, OCI-Ly3 and Balm3 were cultured in exosome-free medium with or without doxorubicin (DXR, 1 µM, 3 h), washed and cultured in fresh exosome-free medium for another 20 hours. The supernatants were collected, exosomes were prepared and the amount of doxorubicin measured by HPLC. SU-DHL-4 cells were treated with DXR (1 µM for 4 h), the plasma membrane stained with anti-CD46-FITC, the cells washed and observed in the immediate wash-out phase (B,C). Confocal imaging detected strong nuclear DXR binding, and areas of DXR accumulation at the outer cell membrane (B, as boxed). Dynamic imaging by TIRF microscopy revealed aggregates of DXR fluorescence to move from the nucleus to the plasma membrane (100x, see box in C as movie).

**Supp. Figure 2. DLBCL *in ovo* xenotransplantation model.** (A) Lymphoma tumor xenograft (arrowhead) on day 10 after implantation after SU-DHL-4 cell implantation on the chorioallantoic membrane (view onto the CAM through window of the chicken egg shell). (B) Canulation of a venous vessel inside the egg with a 32 gauge needle, and intravenous injection of pixantrone (blue fluid). (C) Examples of tumor explants after doxorubicin treatment with or without indomethacin cotreatment.

**Supp. Figure 3. Increased cytotoxicity pixantrone and doxorubicin against DLBCL-ABC cell line OCI-Ly3 by pretreatment with indomethacin.** A) OCI-Ly3 cells were treated with doxorubicin or pixantrone for 3 h with or without indomethacin pretreatment (10 µM, 24 h), and cell viability was assessed after 24 h using MTT. OCI-Ly3 cells were more susceptible to doxorubicin or pixantrone after pretreatment, while indomethacin treatment alone did not affect cell viability (two-way ANOVA. \* p<0.05 \*\* p<0.01). B) Fluorescence analysis of exosomes collected from OCI-Ly3 cells pulsed with a sublethal dose of doxorubicin (1 µM) for 3 h after 6, 12 or 24 h show a strong fluorescence signal at 560nm. C) Indomethacin increases efficacy of doxorubicin and pixantrone *in vivo*. OCI-Ly3 lymphoma cells were seeded on the chorioallantoic membrane of chicken eggs. After 7 days lymphomas were treated with 50 ng doxorubicin (DXR) or pixantrone (Pix) intravenously with or without a topical pretreatment with 1ml of 10 µM indomethacin (Indo) for 24 h, a control was performed with phosphate buffered saline (PBS), as shown above indomethacin alone has no impact on tumor weight after 24 h. Doxorubicin and pixantrone induced lymphoma regression, enhanced by indomethacin pretreatment for both doxorubicin and pixantrone (students t-test, n=3, \* p<0.05, p DXR vs. Indo/DXR: 0.08).

**Supp. Figure 4: Celecoxib and omeprazole do not alter doxorubicin-susceptibility in SU-DHL-4 and OCI-Ly1 cells.** A) Celecoxib does not consistently increase the cytotoxicity of doxorubicin in DLBCL cell lines. The cell lines SU-DHL-4 and OCI-Ly1 were pulsed with doxorubicin for 3 h after pretreatment with celecoxib for 24 h. Cell viability was assessed 24 h after doxorubicin exposure using MTS. While in OCI-Ly1 40 µM celecoxib slightly increased the cytotoxicity (two-way ANOVA and Bonferroni test; p=0.0003) in SU-DHL-4 we did not detect increased cytotoxicity although celecoxib alone showed significant toxicity at 40 µM. B) Omeprazole does not increase the cytotoxicity of doxorubicin in DLBCL cell lines. The cell lines SU-DHL-4 and OCI-Ly1 were pulsed with doxorubicin for 3 h after pretreatment with omeprazole for 24 h. Cell viability was assessed 24 h after doxorubicin exposure using MTS. In both SU-DHL-4 and OCI-Ly1 omeprazole did not increase the cytoxicity of doxorubicin. Of note, in SU-DHL-4 omeprazole significantly decreased the cytotoxicity of doxorubicin (two-way ANOVA and Bonferroni test; p=0.0007).