Lymphomas are sex hormone-regulated malignancies
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Conclusions
Lymphomas are under control of sex hormones. Estrogens have a protective role in lymphoma progression via ERβ signaling. Our results suggest that targeting ERβ could be a new approach in treating lymphomas. In addition, ERβ expression might be used as a prognostic marker.

Introduction
Lymphomas are not generally considered as hormone-related cancers despite that most lymphomas show a clear gender difference in incidence and prognosis. Male sex shows a higher incidence and in general shorter survival.

Aim
To experimentally investigate the endocrine impact, particularly of sex hormones, on the gender difference in lymphoma progression, with the aim to uncover new endocrine molecular targets as future treatment options.

Important results
1. Lymphoma tumors grow faster in male mice vs. female mice, a difference that disappears following ovariectomy (Yakimchuk et al., Leukemia 25:1103-1110, 2011).

2. Androgens also inhibit lymphoma progression, however, not directly but through conversion to estrogens (Talaber et al., Oncotarget 7:20718-27, 2016).

3. Selective ERβ agonist (DPN) treatment significantly inhibits lymphoma proliferation, as well as the survival and maturation of B cells (Yakimchuk et al., Blood 123, 2054-2061, 2014).

4. ERβ agonists (DPN) treatment significantly inhibits the expression of vascularization genes in mice grafted with lymphoma (Yakimchuk et al., Blood 123, 2054-2061, 2014).

5. ERβ agonist (DPN) treatment affects gene expression and signal pathways in Mantle cell lymphoma (Mino cells).

6. A complex association dependent on drug treatment was found between nuclear ERβ expression and prognosis in clinical DLBCL samples (Hasni et al., Leuk Lymphoma 58:418-427, 2017).

RNA-seq analysis of Mantle cell lymphoma tumors (Mino cells) subcutaneously grafted in mice and treated in vivo with the ERβ selective agonist DPN or vehicle, respectively. Up Gene set enrichment analysis of statistically significantly up-regulated and down-regulated pathways in the DPN treated tumors compared with vehicle treatment. Left: Volcano plot showing the differentially expressed mRNAs in the DPN treated tumors compared with the vehicle treated tumors.

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