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Investigating EZH2 as a druggable mediator of immune cell exclusion in desmoid tumors

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Using a genetic CRISPR/Cas9 based desmoid tumor model in the frog *Xenopus tropicalis* we have identified the gene *EZH2*, which encodes a member of the polycomb repressive complex 2 and is thereby involved in epigenetic regulation, as a dependency factor for desmoid tumors. Furthermore, a short (4-week) treatment of *Xenopus* carrying established desmoid tumors with the EZH2 inhibitor Tazemetostat caused a significant reduction in desmoid tumor volume. At the moment the mode of action of Tazemetostat in this anti-tumor response is unknown. Interestingly, we found that Tazemetostat reduces Wnt pathway activity in human desmoid cell cultures but does not have an overt effect on cell proliferation or cell death *in vitro*. Therefore, given the well-established fact that solid tumors in which the Wnt/β-catenin pathway is activated are immunologically cold and thereby insensitive to immune checkpoint inhibition, we postulate that the regression in desmoid tumor volume observed in the *Xenopus* model upon Tazemetostat treatment counters this immune suppressive environment and allows the engagement of a natural anti-tumor immune response. Using a range of genetic experiments in *Xenopus tropicalis* we scrutinize our hypothesis that a reduced Wnt signaling activity upon Tazemetostat treatment alleviates the immune checkpoint controls and allows the occurrence of a T-cell mediated immune response towards the desmoid tumor. An update of these experiments will be presented at the workshop.