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Investigating the mechanisms and tumor-host interactions mediating desmoid tumor regression by EZH2 inhibition in CRISPR-based *Xenopus tropicalis* models

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 four-week treatment of *Xenopus tropicalis* 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, we want to investigate whether the regression of tumor volume by EZH2 inhibition is intrinsic to the tumor cells or is rather due to Wnt-pathway mediated communication of the tumor cells with their microenvironment. Using CRISPR/Cas9 mediated *apc* disruption in *rag2* knockout animals, we are investigating whether the mode of action of EZH2 inhibition involves the engagement of a natural anti-tumor immune response. Finally we will present the use of CRISPR base editors to generate desmoid tumor models via introduction of activating missense mutations in the *ctnnb1* gene.