This abstract was submitted to the DTRF Research Workshop in September, 2020.

Identifying and characterizing dependency factors in a genetic *Xenopus tropicalis* desmoid tumor model

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We developed a fast, semi-high throughput and cheap *Xenopus tropicalis* model for identifying and/or characterizing promising drug targets for treating desmoid tumors. The platform also allows pre-clinical assessment of novel candidate therapeutic compounds. A methodology was developed, called CRISPR/Cas9-mediated Negative Selection Identification of genetic Dependencies (CRISPR-NSID), that allows in vivo elucidation of cancer cell vulnerabilities in genetic cancer models. The methodology uses multiplexed CRISPR/Cas9 based genome editing by simultaneously targeting a tumor suppressor gene (in casu *apc*) and a candidate dependency gene. It thereby exploits the fact that for a genetic dependency there is an incapability for recovering tumors carrying biallelic frameshift mutations in this gene. Using CRISPR-NSID we identified the epigenetic regulator EZH2 and the transcription factor CREB3L1 as genetic dependencies for desmoid tumors. Interestingly, inhibition of the enzymatic activity of EZH2 by the compound Tazemetostat (Tazverik) reduced the size of established desmoid tumors in the *Xenopus* model. We recently introduced magnetic resonance imaging (MRI) to allow longitudinal measurement of drug treatment responses in the model. Finally, we further expanded our *Xenopus* model by inducing the activating S45F point mutation in the *ctnnb1* gene using Cas9 Base Editors.