Discovery of anti-melanoma effect of flubendazole by zebrafish platform.

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Melanoma is one of the most deadly malignant diseases with the highest increase in incidence rate over the past 50 years. Even with new drug applications, its death rates have been stable over this decade. To discover new anti-melanoma drugs, we performed chemical screening using zebrafish melanoma allograft model. For preparing melanoma model of zebrafish, human BRAF mutation (BRAF[V600E]) -driven zebrafish melanoma cells were injected into the circulation of young zebrafish (48 hours-post-fertilization). The melanoma cells increased about 10-times on 6 days after implantation. We tested 2320 chemicals using this allograft zebrafish in combination with the fluorescence plate reader, and found that several chemicals can suppressed melanoma proliferation in vivo. Of these, flubendazole (FLBZ) also suppressed A375 melanoma cell proliferation in mouse xenografts. We further identified that the anti-melanoma function of FLBZ was responsible to inhibition of epithelial-to-mesenchymal transition, not to BRAF mutation or autophagy induction as previously reported. In summary, integrated cross-species analysis using zebrafish, mice and human cells revealed that FLBZ should be one of strong candidates for anti-melanoma drug.