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SUMMARY & MISSION STATEMENT

The goal of our research is to determine molecular mechanisms underlying melanoma initiation, growth, and metastasis formation, with a particular focus on embryonic programs reactivated during tumorigenesis.

OVERVIEW

Tumor cells conceivably share properties with normal cells of the tissue, from which the tumor derives. Melanoma arise from the pigment cell lineage that originates during embryonic development from neural crest stem cells (NCSCs). Our lab has demonstrated that multipotent cells with NCSC properties can be isolated from both human and mouse melanoma biopsies. Intriguingly, interfering with features of normal NCSCs influences tumor growth and invasiveness both in genetic melanoma mouse models *in vivo* and in human melanoma cells. For instance, a transcription factor signature active in NCSCs also appears to regulate 'stemness' properties and invasiveness in melanoma, and signaling pathways normally regulating NCSC fates control melanoma progression. Likewise, epigenetic and metabolic control mechanisms important for proper neural crest development are functionally involved in melanoma progression *in vivo*. Finally, there is increasing evidence that melanoma cells in response to targeted therapy and immunotherapy acquire a NCSC-like state associated with increased resistance. Thus, our research on stem cells during embryonic development provides insights into the biology of melanoma that might ultimately be relevant for treatment.

SELECTED CANCER RELATED PUBLICATIONS

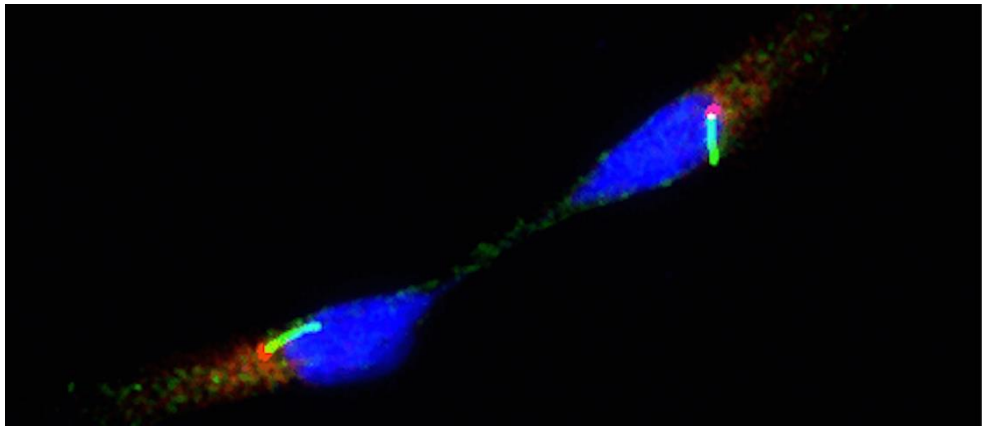
EZH2-mediated primary cilium deconstruction drives metastatic melanoma formation**.** Zingg D, Debbache J, Peña-Hernández R, Antunes AT, Schaefer SM, Cheng PF, Zimmerli D, Haeusel J, Calçada RR, Tuncer E, Zhang Y, Bossart R, Wong KK, Basler K, Dummer R, Santoro R, Levesque MP, and Sommer L. **Cancer Cell**, *in press.*

The low affinity neurotrophin receptor CD271 regulates phenotype switching in melanoma. Restivo G, Diener J, Cheng PF, Kiowski G, Bonalli M, Biedermann T, Reichmann E, Levesque MP, Dummer R and Sommer L. **Nature Communications**, 2017. Dec 7;8(1):1988.

The Histone Methyltransferase Ezh2 Controls Mechanisms of Adaptive Resistance to Tumor Immunotherapy. Zingg D, Arenas-Ramirez N, Sahin D, Rosalia RA, Antunes AT, Haeusel J, Sommer L*, Boyman O. **Cell Reports,** 2017. 20(4):854-867 (*co-corresponding author)

The epigenetic modifier EZH2 controls melanoma growth and metastasis through silencing of distinct tumour suppressors. Zingg D, Debbache J, Schaefer SM, Tuncer E, Frommel SC, Cheng P, Arenas-Ramirez N, Haeusel J, Zhang Y, McCabe MT, Creasy CL, Levesque MP, Boyman O, Santoro R, Shakhova O, Dummer R, and Sommer L. **Nature Communications**, 2015. 6:6051.

Sox10 promotes the formation and maintenance of giant congenital naevi and melanoma. Shakhova O, Zingg D, Schaefer SM, Hari L, Civenni G, Blunschi J, Claudinot S, Okoniewski M, Beermann F, Mihic-Probst D, Moch H, Wegner M, Dummer R, Barrandon Y, Cinelli P, Sommer L. **Nature Cell Biology,** 2012. 14: 882-890.



The primary cilium (green) is a signaling organelle that projects from the surface of many vertebrate cells, including melanocytes and benign nevus cells. The epigenetic modifier EZH2 suppresses primary cilium formation, which transforms benign cells and drives metastatic melanoma (Zingg et al., 2018).