

Project Title:**Counteract Melanoma's next Move: Characterizing TRIB2-mediated Resistance to Therapies**

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Summary: (1000 characters)

Advanced melanoma is the deadliest form of skin cancer for which recently two effective treatment options have improved clinical outcome. However, the majority of patients with metastatic melanoma primarily fail to respond or develop resistance after initial response. Therefore, the identification of molecular mechanisms underlying drug resistance is critical to improve patient outcome and has enormous clinical and economic value. The Link lab has discovered a novel mechanism of resistance to anti-melanoma therapies mediated by the protein TRIB2. With this research proposal, we plan to characterize the molecular mechanisms underlying TRIB2-mediated resistance to anti-melanoma drugs including recently approved MEK inhibitors and determine the clinical relevance of our findings. The execution of the research proposal would lay the groundwork to translate our knowledge into clinically useful tools to improve the treatment of metastatic melanoma.

Bibliographic references:

- Henriques V., Martins M., **Link W.** and Ferreira B.I (2018) The emerging therapeutic landscape of advanced melanoma, *Current Pharmaceutical Design* (accepted with minor changes)
- Hill R., Madureira PA, Ferreira, B, Baptista. I, Machado, S, Colaço L., dos Santos M., Liu N., Dopazo, A, Ugurel S., Adrienn A., Kiss-Toth E., Isbilen M., Gure AO and **Link W.** (2017) TRIB2 confers resistance to anti-cancer therapy by activating the serine/threonine protein kinase AKT. *Nature Comm.* 8, 14687. doi: 10.1038/ncomms14687.
- Link W.** (2017) Mind the gap, see the immuno-connection. *Nature Chem. Biol.* Apr 24. doi: 10.1038/nchembio.2373.

Martins R., Lithgow G.J., **Link W.** (2016) Long live FOXO: Unravelling the role of FOXO proteins in aging and longevity. *Aging Cell* 15, 196-207. doi: 10.1111/ace.12427

Hill R., Kalathur R., Colaço L., Brandão R., Ugurel S., Futschik M. and **Link W.** (2015) TRIB2 as a biomarker for diagnosis and progression of melanoma. *Carcinogenesis* 36, 469-477

Hill R., Kalathur R., Callejas S., Colaço L., Brandão R., Garcia Serelde B., Cebriá A., Blanco-Aparicio C., Pastor J., Futschik M., Dopazo A. and **Link W.** (2014) Genome wide expression profiling in breast cancer following Phosphatidylinositol 3-Kinase (PI3K) inhibition directs p53-independent cell cycle arrest via the differential induction of FOXO-dependent genes. *Breast Cancer Research* 16, 482

Hung M.C. and **Link W.** (2011) Protein localization in disease and therapy. *Journal Cell Science* 124, 3381–3392.

Zanella F., Renner O., García B., Callejas S., Dopazo A., Peregrina S., Carnero A. and **Link W.** (2010) Human TRIB2 is a repressor of FOXO that contributes to the malignant phenotype of melanoma cells. *Oncogene* 29, 2973-2982.