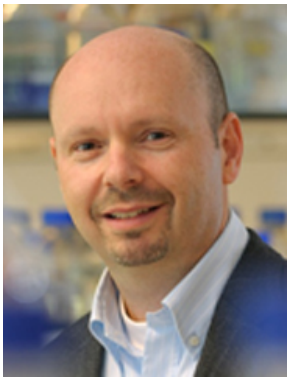
Seminar series FOR2127 – Selection and adaptation during metastatic cancer progression



Thursday, 12 July 2018
Konfernzraum, Biopark III
14.00 h

Dr. Daniel Peeper
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"Towards rational combinatorial cancer treatment – a functional genomics approach"

For a long time, advanced-stage melanomas were refractory to the available therapeutic options, but recent developments have begun offering better perspectives for patients. The small molecule inhibitor vemurafenib, specifically targeting the mutant $BRAF^{V600E}$ kinase, was the first standard of personalized care for patients diagnosed with mutant BRAF metastatic melanoma. Although this compound initially reduces tumor burden dramatically, eventually most melanomas become resistant and progress on treatment. This occurs by the acquisition of additional mutations or other alterations, most of which reactivate the mitogen-activated protein kinase (MAPK) pathway. Although further suppression of BRAF-MAPK signaling by the inclusion of MEK inhibitor delays resistance, eventually most patients relapse.
The clinical outcome of late-stage melanoma patients has also greatly improved thanks to the recent availability of T cell checkpoint modulation, primarily by CTLA-4 and PD-1/PD-L1 blockade. But still, large patient groups fail to (durably) benefit from these treatments, underscoring the continuing need for developing novel therapeutic modalities.
Therefore, in spite of these new perspectives, there is a dire need to identify additional targets amenable to therapeutic intervention, possibly to be used in combination settings with tumor inhibitors alongside immune activators. We are studying (lack of) sensitivity to both tumor and immune cell treatment using patient biopsies, patient-derived xenografts (PDX) and low-passage cell lines. These systems are used for systematic function-based genetic screens to identify melanoma and immune cell factors representing pharmacologically tractable therapeutic targets. The results from these and related studies will be discussed.

Selected reading:

Müller J, Krijgsman O, Tsoi J, Robert L, Hugo W, Song C, Kong X, Possik PA, Cornelissen-Steijger PD, Geukes Foppen MH, Kemper K, Goding CR, McDermott U, Blank C, Haanen J, Graeber TG, Ribas A, Lo RS, Peeper DS. Low MITF/AXL ratio predicts early resistance to multiple targeted drugs in melanoma. Nat Commun.2014 Dec 15;5:5712. doi: 10.1038/ncomms6712. PubMed PMID: 25502142; PubMed Central PMCID: PMC4428333.

Kong X, Kuilman T, Shahrabi A, Boshuizen J, Kemper K, Song JY, Niessen HWM, Rozeman EA, Geukes Foppen MH, Blank CU, Peeper DS. Cancer drug addiction is relayed by an ERK2-dependent phenotype switch. Nature. 2017 Oct 12;550(7675):270-274. doi: 10.1038/nature24037. Epub 2017 Oct 4. PubMed PMID: 28976960; PubMed Central PMCID: PMC5640985.