Feichtner *et al.: Intrinsic Activity*, 2017; **5**(Suppl.1):A4.7
doi:10.25006/IA.5.S1-A4.7
published online: 25 September 2017

INTRINSIC ACTIVITY

23rd Scientific Symposium of the Austrian Pharmacological Society

Innsbruck, 28–29 September 2017

MEETING ABSTRACT

A4.7

Nuclear effectors of oncogenic BRAF signaling and their pharmacological inhibition

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Background: Most key proteins in mitogenic signal transmission and gene regulation are encoded by proto-oncogenes of which many originally had been identified in transforming retroviruses. The BRAF and MYC oncoproteins are master switches in cell proliferation and represent major drivers in human tumorigenesis. Signals transmitted by the BRAF protein kinase are relayed into the nucleus via MAP kinases leading to activation of the transcription factors MYC and AP-1. Similar to MYC, AP-1, consisting mainly of JUN and FOS proteins, has a pivotal role in oncogenic processes leading to malignant cell growth and invasion.

Methods: Using small molecules, we aim to pharmacologically inhibit AP-1, MYC, or upstream-acting regulatory MAP kinases, which could represent a suitable strategy to modulate or even to revert signaling processes leading to the initiation or maintenance of neoplastic cell transformation. For efficient analysis of small organic molecules or peptides for their potentials to interfere with oncogenesis initiated by human BRAF, MYC or AP-1, a cell transformation system was established based on quail embryo fibroblasts (QEF). In these cells, either single or combinatorial oncogene expression leads to efficient cell transformation and tumorigenesis within days, and therefore this system represents a major experimental advantage.

Results: Co-expression of *BRAF* and *MYC* orthologues in avian fibroblasts leads to activation of AP-1 at transcriptional and post-transcriptional levels, suggesting that this transcription factor complex has a crucial role in cell transformation initiated by oncogenic BRAF signaling. Novel promising compounds have emerged in the last years, which specifically interfere with dimer formation between MYC and MAX thereby inhibiting MYC-specific transcriptional regulation and oncogenic transformation [1,2], or selectively inhibiting AP-1. These compounds will be employed either individually or in combination to interfere with growth and viability of therapy-resistant human cancer cells. In addition, specific inhibition of critical AP-1 target gene products could provide an additive value.

Discussion: The identification of compounds selectively interfering with initiation of oncogenic BRAF signaling in cell culture should yield novel targets to attack BRAF-dependent tumorigenesis in cancer types, which have so far remained untreatable by known specific inhibitors.

References

1. Hart JR, Garner AL, Yu J, Ito Y, Sun M, Ueno L, Rhee JK, Baksh MM, Stefan E, Hartl M, Bister K, Vogt PK, Janda KD: **Inhibitor of MYC identified in a Kröhnke pyridine library.** *Proc Natl Acad Sci USA,* 2014; 111(34):12556–12561. doi:10.1073/pnas.1319488111
2. Raffeiner P, Röck R, Schraffl A, Hartl M, Hart JR, Janda KD, Vogt PK, Stefan E, Bister K: ***In vivo* quantification and perturbation of Myc-Max interactions and the impact on oncogenic potential.** *Oncotarget,* 2014; 5(19):8869–8878. doi:10.18632/oncotarget.2588

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