**Supplemental Notes**

**Supplemental Note 1: *Cisplatin-induced specific effects in juvenile wt medaka***

Cisplatin-treated wt fish showed a number of enriched GO terms in the upregulated genes associated with processes of cellular communication like connexon complex (GO:0005922), gap junction (GO:0005921) or transporter activity (GO:0005215) (Table Note 1a\_SuppInfo). Gap junctional communication is mediated by the connexin protein family (Kumar and Gilula 1996; Sohl and Willecke 2004) and the family members *gjc1* (gap junction protein, gamma 1, 45kDa), *gjb3*, *4* and *5* (gap junction protein, beta 3, 31kDa, beta 4, 30.3kDa, beta 5, 31.1kDa) are upregulated in cisplatin-treated wt fish. Upregulation of these genes together with the above-mentioned enriched GO terms may indicate a general cytotoxic effect of cisplatin. Our findings fit to studies with mammalian cells that show a link between gap junctions and toxicity of cisplatin (Jensen and Glazer 2004; Huang and Tan 2012). At the same time, the peptidyl arginine deiminase genes, type I, II and III (*padi1*, *padi2* and *padi3*), which are responsible for the post-translational deamination of arginine to citrulline (Rogers and Taylor 1977; Vossenaar *et al.* 2003) are highly enriched in the overrepresented GO terms (e.g. `peptidyl-citrulline biosynthetic process from peptidyl-arginine` (GO:0018101), `citrulline biosynthetic process` (GO:0019240)) in the cisplatin-treated wt medaka (Table Note 1a\_SuppInfo). These genes are expressed in the epidermis (Mechin *et al.* 2005) targeting on cytoskeletal and cytoskeleton-associated proteins in the skin (Ying *et al.* 2009). Their upregulation could be a reaction to cisplatin treatment in the healthy wt fish. In humans, cisplatin induces oxidative stress and inflammatory processes (Yao *et al.* 2007) that can also cause an increased expression of the *padi1*, *2* and *3* genes. We conclude that cisplatin-caused inflammatory processes lead to an increase of *padi1*, *2*, *3* gene expression in the cisplatin-supplemented wt medaka.

The downregulated genes for example genes of potassium voltage-gated channels of subfamily G (*kcng2*, *kcng3*, *kcng4*) showed enriched GO terms associated with channel activity (e.g. `ion channel activity` (GO:0005216) or `synaptic transmission` (GO:0007268)) (Table Note 1b\_SuppInfo).

**Supplemental Note 2: *Trametinib-induced effects on juvenile wt medaka***

In trametinib-treated wt fish compared to DMSO-treated wt fish, we identified an overrepresentation of genes, which are involved in stimulus-response processes serving as `proof of principle` for the absorption and metabolization of trametinib. Further upregulated genes are related to inflammation and immune system (Table Note 2a\_SuppInfo). Among the upregulated genes of enriched GO terms, some interesting candidate genes were detected, e.g. the drug transporter *abca1* (ATP-binding cassette, sub-family A, member 1) or *tnfaip3* (tumor necrosis factor, alpha-induced protein 3). *abca1* belongs to the family of ATP-binding cassette transporters, which are involved in the transport of substrates and drugs across cellular and organelle membranes. Trametinib treatment induced in wt medaka a reducedexpression of genes associated with cellular processes. Ribosomal proteins like *s21*, *l35a* or *l22* (*rps21*, *rpl35a*, *rpl22*) included in three enriched GO terms ((GO:0022626), (GO:0005840), (GO:0044391)) and in the KEGG Pathway `Ribosome` (ID:03010) are indispensable for the assembly of ribosomes and the synthesis of proteins (Table Note 2b\_SuppInfo, Note 2c\_SuppInfo). These processes are closely related to cellular growth and organismal development for instance RPL29 (ribosomal protein L29) null mice have a reduced body weight at birth along with diminished postnatal viability and the RPL29 null mice embryonic fibroblasts show reduced cell proliferation and protein synthesis (Kirn-Safran *et al.* 2007). In addition, a complete loss of RPS19 (ribosomal protein S19) (-/-) in mice leads to an embryonic lethal effect (Matsson *et al.* 2004). Since the ribosomal proteins in the wt samples are not deregulated in the solvent-treated fish, our data suggest a trametinib-induced inhibitory effect on protein synthesis, which can be interpreted as a sign of general unspecific cellular damage.

**References**

Huang, C. Y., and T. H. Tan, 2012 DUSPs, to MAP kinases and beyond. Cell Biosci 2**:** 24.

Jensen, R., and P. M. Glazer, 2004 Cell-interdependent cisplatin killing by Ku/DNA-dependent protein kinase signaling transduced through gap junctions. Proc Natl Acad Sci U S A 101**:** 6134-6139.

Kirn-Safran, C. B., D. S. Oristian, R. J. Focht, S. G. Parker, J. L. Vivian *et al.*, 2007 Global growth deficiencies in mice lacking the ribosomal protein HIP/RPL29. Dev Dyn 236**:** 447-460.

Kumar, N. M., and N. B. Gilula, 1996 The gap junction communication channel. Cell 84**:** 381-388.

Matsson, H., E. J. Davey, N. Draptchinskaia, I. Hamaguchi, A. Ooka *et al.*, 2004 Targeted disruption of the ribosomal protein S19 gene is lethal prior to implantation. Mol Cell Biol 24**:** 4032-4037.

Mechin, M. C., M. Enji, R. Nachat, S. Chavanas, M. Charveron *et al.*, 2005 The peptidylarginine deiminases expressed in human epidermis differ in their substrate specificities and subcellular locations. Cell Mol Life Sci 62**:** 1984-1995.

Rogers, G. E., and L. D. Taylor, 1977 The enzymic derivation of citrulline residues from arginine residues in situ during the biosynthesis of hair proteins that are cross-linked by isopeptide bonds. Adv Exp Med Biol 86A**:** 283-294.

Sohl, G., and K. Willecke, 2004 Gap junctions and the connexin protein family. Cardiovasc Res 62**:** 228-232.

Vossenaar, E. R., A. J. Zendman, W. J. van Venrooij and G. J. Pruijn, 2003 PAD, a growing family of citrullinating enzymes: genes, features and involvement in disease. Bioessays 25**:** 1106-1118.

Yao, X., K. Panichpisal, N. Kurtzman and K. Nugent, 2007 Cisplatin nephrotoxicity: a review. Am J Med Sci 334**:** 115-124.

Ying, S., S. Dong, A. Kawada, T. Kojima, S. Chavanas *et al.*, 2009 Transcriptional regulation of peptidylarginine deiminase expression in human keratinocytes. J Dermatol Sci 53**:** 2-9.