Neuroblastoma treatment using synergistic inhibition of histone deacetylases 8/10 and ALK (P-1159)

Key facts

- New combination of HDAC 8/10 and ALK inhibitors shows synergistic effect for more efficient neuroblastoma therapy
- The combination can overcome single substance drug resistance.

Abstract
Neuroblastoma is the most common type of cancer in infancy and the third most common childhood cancer. Besides other currently available treatment options, trials are under way to investigate the efficacy of broad-spectrum histone deacetylase (HDAC) inhibitors, such as vorinostat, which unfortunately still have toxic side effects. The present invention shows that a combination of HDAC and ALK inhibitors is surprisingly synergistic and can additionally overcome single substance drug resistance.

Development Stage
The *in vitro* tested method was successfully verified with neuroblastoma cell lines. In addition, the findings were compared with the expression profiling of microarray data from neuroblastoma patients. The latter data show that patients who simultaneously express high levels of HDAC8 and HDAC10 have significantly poorer outcomes than patients who express either HDAC 8 or 10 alone at a high level.

The Technology
Inhibiting HDAC8 in neuroblastoma cells slows their growth, leads to differentiation and, ultimately, cell death. Targeting HDAC10 with inhibitors or knockdown inhibits autophagy, which sensitizes cells to conventional chemotherapy and also leads to cell death. While these two enzymes have individually important roles, using single inhibitors requires high doses to achieve the outcomes necessary to successfully combat the tumor. Additionally, the likelihood of resistance developing is higher and is likely to occur more quickly with single-agent therapy.

In vitro experiments combining inhibitors of HDAC8 with inhibitors of either HDAC10 or ALK showed a more than additive effect of these combinations on neuroblastoma cells. This indicates that these combinations can be used to treat neuroblastoma or other tumors more effectively than with single substances.

Applications and Commercial Opportunity
DKFZ is looking for a commercial partner to establish this new treatment modality in clinical practice.

Inventors
The investigators are: Jing Shen, Emily Koeneke, Olaf Witt, Annette Kopp-Schneider, and Ina Oehme. All inventors are employed at the DKFZ.

Intellectual Property
An European patent application “Therapeutic combinations for use against neuroblastoma” has been filed EP 14166679.2 with a priority date of April 30th in 2014

References

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Further Information

No other public information is currently available, but further information (speaking with the inventor) is available under a signed Confidential Disclosure Agreement (CDA).

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