Development of small molecule miR-17-92 inhibitors

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MicroRNAs (miRNAs) are conserved small non-coding RNAs that regulate gene expression at the posttranscriptional level by pairing to the 3' UTR of other genes. miR-17-92 is a key regulator of lymphocyte biology, controlling e.g. cell proliferation, survival as well as differentiation and function of different T cell subsets. miR-17-92 is amplified in human lymphomas and other malignancies and is also involved in additional disorders including immune, cardiovascular and neurodegenerative diseases as well as in aging.

Given the importance of miR-17-92 in such a variety of diseases we aim at exploiting it as a therapeutic target. miRNAs can be inhibited through the administration of nucleotide-based inhibitors. Major disadvantages are their transient effect, instability and poor in vivo delivery. In contrast, small molecules permeate cells easily, are intracellularly stable and large libraries are available for high-throughput screening. We screened 60'000 compounds using a luciferase reporter assay and identified small molecules which modulate miR-17 reporter activity. Treatment of mouse naïve CD4 or CD8 T cells with one of the hit compounds resulted in similar phenotypes as in miR-17-92 deficient mice (different target derepression and reduced in vitro T cell differentiation). Screening of 172 chemically related compounds identified 2 analogs with improved potency. Treatment of primary human CD4 or CD8 cells as well as different tumor cell lines overexpressing the miR-17-92 cluster resulted in reduced proliferation and activation and increased cell death.

We are currently analyzing RNA-seq (transcriptome and small RNA) data to investigate the specificity of the compounds for miR-17. In addition, we are validating the disease relevance of the compounds first in vitro and then in vivo using different lymphoma cell lines and mouse lymphoma models. In summary, in a luciferase-based screen, we identified potential miR-17-92 inhibitors that phenocopy in T cells the changes observed in miR-17-92-deficient cells. In addition, preliminary data obtained in lymphoma cell lines showed a preference of the compounds to kill cells overexpressing the miR-17-92 cluster. Overall, the data obtained provide important information to evaluate the potential of the compounds to serve as lead structures for further development as drug candidates.