REALIZING THE BENEFITS OF GENE SILENCING – NOVEL HDAC6 INHIBITOR FOR THE TREATMENT OF INFLAMMATORY DISEASES

HINTERGRUND

Inhibiting the action of histone deacetylases (HDAC) has emerged as a promising therapeutic approach in the treatment of many disorders, e.g. hematopoietic malignancies, with several selective HDAC inhibitors (HDACi) already approved for the clinic. The balance between histone acetylation and deacetylation is a critical determinant for cell proliferation, cell-cycle regulation and apoptosis with mutations in genes encoding HDACs linked to aberrant gene expression. Supporting their known anti-inflammatory action is data suggesting their use in the treatment of chronic immune and inflammatory disorders such as rheumatoid arthritis. Here, current treatment regimens have limited efficacy, e.g. first-line NSAIDs (non-steroidal anti-inflammatory drugs) and severe side-effect profiles in the long-term, e.g. steroids. With its two functional catalytic domains and specific physiological roles, HDAC6 presents a promising therapeutic candidate.

LÖSUNG

We present Marbostat-100 as a new class of small molecule inhibitors of HDAC6. Marbostat-100 exhibits superior potency and specificity compared to HDAC6i Tubastatin A and pan-HDACi LBH589. In vivo data from an arthritis mouse model shows a significantly improved therapeutic response without any toxic side effects.

Treatment lowered the clinical score with reduced synovial inflammation and delayed cartilage degradation and bone erosion. Its mode of action is restricted to inhibiting enzymatic activity thereby not destroying the protein.
VORTEILE

- Potent anti-inflammatory and anti-rheumatic effects as alternative to NSAIDs
- Superior potency and specificity compared to competitive products
- Selective inhibition of enzymatic activity limits potential off-site effects
- Water solubility allows for oral application