Realizing the benefits of gene silencing – Novel HDAC6 inhibitor for the treatment of inflammatory diseases

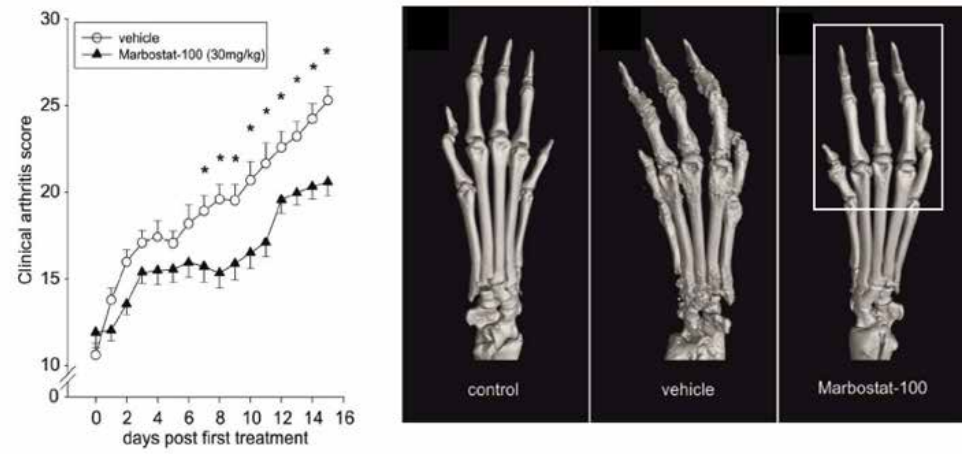
Reference No: B73271*, B77007**

CHALLENGE

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.

INNOVATION

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[1]. Its mode of action is restricted to **inhibiting enzymatic activity** thereby not destroying the protein.

COMMERCIAL OPPORTUNITIES

- 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

DEVELOPMENT STATUS

Enantiomer testing and oral administration currently undergoing[2]
Opportunities for partners:

- Testing the therapeutic range and toxicity in different animal models
- Pharmacologic analysis of underlying molecular mechanism

REFERENCES:

1. J Med Chem. 2018 Apr 26;61(8):3454-3477. doi: 10.1021/acs.jmedchem.7b01593. Epub 2018 Apr 6.
2. Arch Pharm (Weinheim). 2019 Jun;352(6):e1900026. doi: 10.1002/ardp.201900026. Epub 2019 May 6.

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