

Targeting Histone Deacetylases to Suppress Bone Loss in Similar Chronic Inflammatory Diseases, Periodontitis and Rheumatoid Arthritis

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Table of Abbreviations

HDAC	Histone deacetylase
HAT	Histone acetyltransferase
HDACi	Histone deacetylase inhibitors
PD	Periodontitis
RA	Rheumatoid arthritis
TNF- α	Tumour necrosis factor alpha
IL	Interleukin
M-CSF	Macrophage colony stimulating factor
RANKL	Receptor activator of nuclear factor kappa B ligand
RANK	Receptor activator of nuclear factor kappa B
NFATc1	Nuclear Factor of Activated T cells
NF- κ B	Nuclear factor kappa B
OPG	Osteoprotegerin
TRAF-6	TNF receptor factor-6
AP-1	Activator protein-1
IKK	I κ B kinase
CTR	Calcitonin receptor
TRAP	Tartrate Resistant Acid Phosphatase
OSCAR	Osteoclast-associated receptor
CAIA	Collagen antibody induced arthritis
LPS	Lipopolysaccharide
Micro CT	Micro Computed Tomography
DMARDs	Disease modifying anti-arthritic drugs
MTX	Methotrexate

Cath-K	Cathepsin K
mAb	Monoclonal antibody
SAHA	Suberoylanilide hydroxamic acid
TSA	Trichostatin A
PBMCs	Peripheral blood mononuclear cells
MCP-1	Monocyte Chemotactic Protein 1
MIP-1 α	Macrophage Inflammatory Protein 1 α
CIA	Collagen induced arthritis
PTH	Parathyroid hormone
IFN- β	Interferon Beta
IFN- γ	Interferon Gamma
LPS	Lipopolysaccharide
MMP	Matrix metallo-proteinase
BMD	Bone mineral density

Abstract

Rheumatoid arthritis (RA) and periodontitis are two common chronic inflammatory diseases characterized by soft tissue inflammation and associated bone loss. Despite the high prevalence of these conditions and our growing knowledge of the mechanisms involved in the disease processes, the control of bone destruction is still a challenging problem. For this reason it is important to identify anti-resorptive agents that may also inhibit inflammation which can be delivered orally upon diagnosis. Histone deacetylase inhibitors (HDACi) are one such potential therapeutic agent. The aim of this research was to use *in vitro* human peripheral blood mononuclear cells and human osteoclast assays in conjunction with animal models of periodontitis and inflammatory arthritis to determine the effects of novel HDACi (1179.4b which targets class I and II HDACs and NW-21 targets HDAC 1) on both inflammation and bone loss. The results of this thesis have identified that both RA and periodontitis are interrelated diseases, however, the specific HDACs involved in regulating the inflammatory and resorptive processes may be distinct. It is evident that, in arthritis, HDAC 1 is important in tissue inflammation, in periodontitis HDAC 1, 5, 8 and 9 are important and in osteoclasts HDAC 5 and 8 are up regulated. HDACi such as 1179.4b, NW-21 and MS-275 (class I specific HDACi) have been shown to have the potential to treat inflammatory bone loss. Further studies are necessary to elucidate the roles of each HDAC in RA and periodontitis and better target HDACi therapy.

Student Declaration

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution to Melissa Cantley and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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***Inhibitors of histone deacetylases in Class I and Class II suppress human osteoclasts in vitro.** MD Cantley, DP Fairlie, PM Bartold, KD Rainsford, GT Le, AJ Lucke, CA Holding, DR. Haynes. *Journal of Cellular Physiology* 2011;226(12):3233-41

Histone deacetylase inhibitors and periodontal bone loss. MD Cantley, PM Bartold, V Marino, DP Fairlie, GT Le, AJ Lucke, DR Haynes. *Journal of Periodontal Research* 2011;46(6):697-703

Pre-existing periodontitis exacerbates experimental arthritis in a mouse model. MD Cantley, DR Haynes, V Marino, PM Bartold. *Journal of Clinical Periodontology* 2011;38:532-541

Histone deacetylase inhibitors as suppressors of bone destruction in inflammatory diseases. MD Cantley, PM Bartold, DP Fairlie, KD Rainsford, DR Haynes. *J Pharmacy and Pharmacology* 2012;64(6):763-74

Epigenetic regulation of inflammation: progressing from broad acting histone deacetylase (HDAC) inhibitors to targeting specific HDACs. MD Cantley, DR Haynes. *Inflammopharmacology* 2013;21(4):301-7.

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Chapter 2. Pre-existing periodontitis exacerbates experimental arthritis in a mouse model.

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Chapter 4. Histone deacetylase inhibitors and periodontal bone loss.

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Journal of Periodontal Research 2011;46(6):697-703

Chapter 5. Class I and I histone deacetylase (HDAC) expression in human periodontitis.

MD Cantley, TN Crotti, PM Bartold, DR Haynes.
(Manuscript in preparation)

Chapter 6. Targeting HDAC 1 to suppress both inflammation and bone loss in arthritis.

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Papers Included in Appendices

Appendix 1. Histone deacetylase inhibitors as suppressors of bone destruction in inflammatory diseases.

MD Cantley, PM Bartold, DP Fairlie, KD Rainsford, DR Haynes.
J Pharmacy and Pharmacology 2012;64(6):763-74

Appendix 2. Epigenetic regulation of inflammation: progressing from broad acting histone deacetylase (HDAC) inhibitors to targeting specific HDACs.

MD Cantley, DR Haynes.
Inflammopharmacology 2013;21(4):301-7.