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

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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>HDAC</td>
<td>Histone deacetylase</td>
</tr>
<tr>
<td>HAT</td>
<td>Histone acetyltransferase</td>
</tr>
<tr>
<td>HDACi</td>
<td>Histone deacetylase inhibitors</td>
</tr>
<tr>
<td>PD</td>
<td>Periodontitis</td>
</tr>
<tr>
<td>RA</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Tumour necrosis factor alpha</td>
</tr>
<tr>
<td>IL</td>
<td>Interleukin</td>
</tr>
<tr>
<td>M-CSF</td>
<td>Macrophage colony stimulating factor</td>
</tr>
<tr>
<td>RANKL</td>
<td>Receptor activator of nuclear factor kappa B ligand</td>
</tr>
<tr>
<td>RANK</td>
<td>Receptor activator of nuclear factor kappa B</td>
</tr>
<tr>
<td>NFATc1</td>
<td>Nuclear Factor of Activated T cells</td>
</tr>
<tr>
<td>NF-κB</td>
<td>Nuclear factor kappa B</td>
</tr>
<tr>
<td>OPG</td>
<td>Osteoprotegerin</td>
</tr>
<tr>
<td>TRAF-6</td>
<td>TNF receptor factor-6</td>
</tr>
<tr>
<td>AP-1</td>
<td>Activator protein-1</td>
</tr>
<tr>
<td>IKK</td>
<td>IκB kinase</td>
</tr>
<tr>
<td>CTR</td>
<td>Calcitonin receptor</td>
</tr>
<tr>
<td>TRAP</td>
<td>Tartrate Resistant Acid Phosphatase</td>
</tr>
<tr>
<td>OSCAR</td>
<td>Osteoclast-associated receptor</td>
</tr>
<tr>
<td>CAIA</td>
<td>Collagen antibody induced arthritis</td>
</tr>
<tr>
<td>LPS</td>
<td>Lipopolysaccharide</td>
</tr>
<tr>
<td>Micro CT</td>
<td>Micro Computed Tomography</td>
</tr>
<tr>
<td>DMARDs</td>
<td>Disease modifying anti-arthritis drugs</td>
</tr>
<tr>
<td>MTX</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Term</td>
<td>Abbreviation</td>
</tr>
<tr>
<td>--------</td>
<td>------------------</td>
</tr>
<tr>
<td>Cath-K</td>
<td>Cathepsin K</td>
</tr>
<tr>
<td>mAb</td>
<td>Monoclonal antibody</td>
</tr>
<tr>
<td>SAHA</td>
<td>Suberoxylanilide hydroxamic acid</td>
</tr>
<tr>
<td>TSA</td>
<td>Trichostatin A</td>
</tr>
<tr>
<td>PBMCs</td>
<td>Peripheral blood mononuclear cells</td>
</tr>
<tr>
<td>MCP-1</td>
<td>Monocyte Chemotactic Protein 1</td>
</tr>
<tr>
<td>MIP-1α</td>
<td>Macrophage Inflammatory Protein 1α</td>
</tr>
<tr>
<td>CIA</td>
<td>Collagen induced arthritis</td>
</tr>
<tr>
<td>PTH</td>
<td>Parathyroid hormone</td>
</tr>
<tr>
<td>IFN-β</td>
<td>Interferon Beta</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>Interferon Gamma</td>
</tr>
<tr>
<td>LPS</td>
<td>Lipopolysaccharide</td>
</tr>
<tr>
<td>MMP</td>
<td>Matrix metallo-proteinase</td>
</tr>
<tr>
<td>BMD</td>
<td>Bone mineral density</td>
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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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**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


Signed: M Cantley

Witnessed: M Cantley

Date: / /2013
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List of Jointly Authored Papers Included in Thesis

Chapter 2. 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

Chapter 3. 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

Chapter 4. Histone deacetylase inhibitors and periodontal bone loss.
*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.
**MD Cantley**, DP Fairlie, PM Bartold, V Marino, DR Haynes.
(Manuscript in preparation)

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.