

# A Historical Perspective: the Role of Interleukin-1 Receptor Antagonist (IL-1Ra) in the Pathogenesis of Rheumatoid Arthritis

1985

**In vivo observation of an IL-1 inhibitor in humans:** an inhibitor of collagenase and PGE<sub>2</sub> activity, induced by IL-1, is identified in urine of a patient with monocytic leukaemia<sup>1</sup>

**In vitro observation of an IL-1 inhibitor in human cell culture:** an inhibitor of chondrocyte and thymocyte responsiveness to IL-1 is identified in cultured human monocytes<sup>2</sup>

1987

**Description of receptor antagonist mechanism of action of IL-1 inhibitor:** a novel inhibitor of IL-1 bio-activity and ligand binding is identified in the urine of febrile patients<sup>3</sup>

**Clinical observations suggesting an inhibitor to IL-1 activity in disease:** high concentrations of an inhibitor to IL-1 activity are observed in febrile patients and low concentrations in afebrile patients with systemic juvenile rheumatoid arthritis<sup>4</sup>

1990

**IL-1Ra is partially purified from the urine of afebrile patients<sup>5</sup>**

**IL-1Ra is cloned and characterised:** IL-1Ra complementary DNA is obtained from a human monocyte library<sup>6</sup>; IL-1Ra is purified from cultured human monocytes and found to have no agonistic activity at the IL-1 receptor<sup>7</sup>

**Endogenous and recombinant IL-1Ra are observed to inhibit IL-1-mediated bone resorption and PGE<sub>2</sub> production in vitro systems<sup>8</sup>**

1991

**Recombinant IL-1ra is shown to inhibit joint swelling in a murine model of arthritis<sup>9</sup>**

**Recombinant IL-1ra enters clinical trials in patients with rheumatoid arthritis<sup>10</sup>**

1992

**Endogenous IL-1Ra gene expression and protein production is detected in synovial tissues from humans with rheumatoid arthritis<sup>11, 12</sup>:** the protein is localised to the synovial sublining layer and, to a lesser degree, the intimal lining layer in rheumatoid arthritis patients, with macrophage-like synovio-cytes being the major cells containing the immuno-reactive protein. IL-1Ra is virtually undetectable at the cartilage-pannus junction. Messenger RNA for the protein is primarily localised to perivascular lymphoid aggregates

## References

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