

# Synovitis – an inflammation of joints destroying the bone

## How the pioneer work by Dr Barry Bresnihan influenced our understanding on the immune-bone axis

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### Summary

This article is to share some of the key scientific insights made by Dr Barry Bresnihan in rheumatoid arthritis. Dr Bresnihan elaborated new and visionary concepts in arthritis research, which still influence current thinking. He had been particularly dedicated to investigate the inflammatory tissue (synovitis) in RA, which he considered as a clue to understand the pathogenesis of this disease. He thereby pioneered the concept of synovial biopsy as a technique, which allows to directly analyse synovitis and has stimulated many other rheumatologists in joining his efforts. He was also dedicated to understand why synovitis triggers bone destruction in joints and started to work on defining the molecular interactions between inflammation and the bone. This article picks up some of the major insights achieved by Dr Bresnihan's work and how these findings influenced today's understanding of arthritis.

**Key words:** *synovitis; rheumatoid arthritis; inflammation*

### Introduction

This article is to share some of the key scientific insights made by Dr Barry Bresnihan in rheumatoid arthritis (RA). RA is the most severe inflammatory joint disease and one of the most frequent autoimmune diseases in humans [1]. Dr Bresnihan was a physician and rheumatologist dedicated to science aiming to better understand inflammation and autoimmunity in RA. He elaborated new and visionary concepts in arthritis research, which still influence current thinking. Dr. Bresnihan had been particularly dedicated to investigate the inflammatory tissue (synovitis) in RA, which he considered as a clue to understand the pathogenesis of this disease. He thereby pioneered the concept of synovial biopsy as a technique, which allows to directly analyse synovitis and has stimulated many other rheumatologists in joining his efforts. He was also dedicated to understand why synovitis triggers bone destruction in joints

and started to work on defining the molecular interactions between inflammation and the bone. Later, a new research field ("osteimmunology") developed, which has strongly influenced the concepts on the regulation of bone mass in humans [2]. This article (based on the Barry Bresnihan Memorial Lecture [3]) picks up some of the major insights achieved by Dr Bresnihan's work and how these findings influenced today's understanding of arthritis.

### Is a clinically inconspicuous joint indeed normal?

More than 20 years ago, Dr Bresnihan suggested that clinical investigation of the joint might not suffice to pick up pathology [4, 5]. He suspected that even clinically normal joints may not be completely normal, but subclinical inflammatory changes may occur. He was indeed able to detect synovial hyperplasia as well as infiltration of mononuclear cells including T lymphocytes in the synovial tissue of unaffected joints in patients with RA. These findings stimulated new pathophysiological concepts suggesting that the disease may start even before the onset of clinically symptoms [6]. This concept has later been confirmed by several studies suggesting that autoantibody formation as well as synovial changes precede clinical onset of the disease [7]. Similarly, they were also substantiated by the observations that RA patients in clinical remission can show residual synovitis in the imaging [8].

The notion of subclinical disease by Dr Bresnihan was made long before the molecular interactions between the immune system and bone had been unraveled. In fact, he showed that all pre-requisites for osteoclast differentiation can be found in the clinically unapparent joint. Thus synovial hyperplasia and T cell infiltrates, which were found in subclinical synovitis are a source for RANKL and infiltrating monocytes serve as the precursor cells for the osteoclast [9]. Importantly, bone erosions can develop even in the absence of clinically manifested arthritis, which is most likely due to subclinical synovitis in those joints later developing bone damage. Moreover, bone damage in the

absence of major signs of inflammation can be also due to the fact that autoantibodies against citrullinated proteins directly stimulate osteoclastogenesis [10]. Based on the insights on subclinical synovitis and the very early emergence of autoantibodies against citrullinated proteins and bone loss in RA, we now think that autoimmunity as well tiny inflammatory changes suffice to trigger bone loss in RA. This concept is also in accordance with the observation that even small increases of the ultrasensitive C-reactive protein are an independent risk factor for fracture [11].

### What is synovitis?

Another major research achievement of Dr Bresnihan was the detailed deciphering of the different aspects of synovial pathology. He unraveled that synovitis is in fact not just pure infiltration of the joint tissue by immune cells but a much more complex process, which consists of mononuclear immune cell infiltration on the one hand but also profound remodeling of the tissue architecture such as synovial lining layer hyperplasia, fibrosis and vasculogenesis on the other hand. These observations are of seminal importance for understanding the disease process of RA. Such architectural changes may essentially determine the chronicity of the RA disease process.

Thus, alterations of the tissue architecture allows continuous recruitment of immune cells to the synovial tissue by chemokine- chemokine receptor interaction as well as the formation of lymphoid follicles in the synovium and the adjacent bone marrow [12]. It is the deleterious combination between monocyte infiltration, lymphoid follicle formation and synovial hyperplasia, which provides optimal microenvironment to stimulate generation of bone resorbing osteoclasts by providing (1.) sufficient osteoclast precursor cell migration and accumulation in the joint, (2.) autoantibody formation in the lymphoid follicle, which allows stimulation of bone resorbing cells and (3.) abundant expression of RANKL due to synovial hyperplasia. Thus synovial tissue changes in rheumatoid arthritis provide an ideal environment for the generation of bone resorbing cells, which explains the fast degradation of periarticular bone in RA patients.

### What is the mechanism of bone destruction in RA?

Based on this knowledge on the pathogenesis of synovitis Dr Bresnihan formulated new concepts of how synovitis leads to bone destruction. He observed that macrophages accumulate at the cartilage-pannus junction of the joint, which is exactly the place, where bone damage starts [13, 14]. In fact, these cells have later been identified as osteoclasts by Drs Gravalles and Goldring [15]. In fact, osteoclasts are nothing other than specifically differentiated multinucleated macrophages dedicated to resorb bone. Dr. Bresnihan also noted that these macrophages show a phenotype different from that of the macrophages in the synovial lining layer. This notion is not surprising in knowledge of the phenotype of osteoclasts as they are bigger than normal macrophages and also multinucleated but show addi-

tional qualitative changes on their surface such as a ruffled membrane.

Osteoclasts also express large amounts of enzymes such as cathepsins and matrix metalloproteinases in order to degrade the bone matrix. In fact, high-level enzyme expression is exactly the macrophage phenotype, which has been described by Dr. Bresnihan [16]. Such cells are localised close to the bone surface in patients with RA. Furthermore, he found that the number of macrophages in the synovial membrane is correlated with the degree of joint damage, which makes sense as these cells represent either osteoclast precursors or osteoclasts. These findings strongly supported previous data by Dr Dayer highlighting the cytokine production by macrophages is the major source for enzyme production in the synovial membrane [17]. In fact, the later discovery of osteoclasts in the synovial tissue of RA patients as well as expression of molecules such as RANKL, were the logical consequence of these detailed investigations of synovitis of RA patients.

In summary, Dr Bresnihan's work, dedicated to unravel the mechanism of synovitis, has strongly influenced the understanding of immune-bone interaction in rheumatoid arthritis. We now consider the clinical relevance of the cross-talk between the immune and the skeletal system in inflammatory diseases like rheumatoid arthritis. Bone loss during inflammation has now a molecular basis and the clinical changes in patients with rheumatoid arthritis has become a paradigm for the new research field of osteoimmunology.

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