Writing a review article
Personal experience

EPEMY Congress, Sep 2022
MJR workshop

Δαούσης Δημήτρης
Αναπλ. καθηγητής Παθολογίας/Ρευματολογίας
Ιατρική Σχολή Πανεπιστημίου Πατρών

My first review article

- Part of my PhD (Study of CD40L expression on T cells in pts with PsA)
- PubMed based literature review
- Use of key words CD40L and rheumatic diseases, autoimmunity……
- Selection of articles based solely on personal opinion

CLINICAL AND DIAGNOSTIC LABORATORY IMMUNOLOGY, July 2004, p. 635–641 Vol. 11, No. 4
1071-412X/04/$08.00+0 DOI: 10.1128/CDLI.11.4.635–641.2004

MINIREVIEWS

Targeting CD40L: a Promising Therapeutic Approach

Dimitris Daoussis, Andrew P. Andonopoulos, and Stamatis-Nick C. Liossis*

Division of Rheumatology, Department of Internal Medicine, Patras University Hospital, University of Patras Medical School, Patras, Greece

- No abstract!
- No Methods!

- 101 citations since 2004

Targeting CD40L: a Promising Therapeutic Approach

Dimitris Daoussis, Andrew P. Andonopoulos, and Stamatis-Nick C. Liossis*

Division of Rheumatology, Department of Internal Medicine, Patras University Hospital, University of Patras Medical School, Patras, Greece

The activation of lymphocytes is a central event of the adaptive immune response. Physiologically, this activation is carefully controlled. Productive stimulation of T cells is necessary for all T-cell-dependent immune responses and requires two distinct intracellular signals.

The first signal is antigen specific; it is delivered via the antigen-specific T-cell surface receptor (TCR) when antigen is properly presented to the T cell in the context of major histocompatibility complex molecules, found on the cell membrane of antigen-presenting cells (APC). APC are not just passive antigen presenters but they are also responsible for providing the second signal. This second signal is necessary for full and productive T-cell activation, and the process is referred to as costimulation. Occupancy of the TCR alone without a costimulatory signal does not lead to productive T-cell activation. Such T cells are unable to sustain proliferation and often undergo apoptosis, fail to produce cytokines, and become unresponsive to subsequent activation, entering a state called anergy. Initially, it was thought that soluble factors, such as cytokines, were the key transmitters of costimulatory signals. Later, it became apparent that costimulation is a cognate process. Costimulatory signals are delivered through the interaction of several receptor-ligand pairs of cell surface molecules between the T cell and the APC.

Costimulation is a fail-safe mechanism of the immune system to prevent unnecessary lymphocyte activation and works at multiple levels. It allows full activation, prevents anergy or apoptosis, induces differentiation to effector or memory status, sustains cell proliferation, and allows cell-cell cross talk and cooperation. This cross talk between the T cell and the APC is accomplished by receptor-ligand pairs on their cell surfaces, allowing bidirectional communication between participating cells. The first cell surface pair of molecules shown to have costimulatory function was the CD28-B7 pair. Several other pairs of cell surface molecules including CD40-CD40 ligand (CD40L), CD2-CD58, CD11-CD18/ICAM-1, and VLA4-VCAM were described later (17). In this report, we review the importance of the costimulatory signals delivered via the CD40-CD40L pair of molecules.

CD40L is a member of the tumor necrosis factor (TNF) family of cell surface interaction molecules. It is a 261-amino-acid type II membrane glycoprotein, and its expression is mainly confined to the $CD4^+$-T-cell subset. CD40L expression is induced shortly after T-cell activation and represents an early activation marker of T lymphocytes. CD40 is constitutively expressed mainly on B cells, macrophages, and dendritic cells (10). The CD40-CD40L pathway has been extensively investigated and has been shown to play multiple functional roles in the healthy immune system. It enhances the antigen-specific T-cell response through the activation of dendritic cells and the induction of interleukin 12 (IL-12) production by these cells to focus the immune response on the antigen that has engaged the TCR (6, 16, 24, 50, 57). It sustains this response for as long as the antigen remains in the system, and it induces effector functions of interacting $CD40^+$ target cells. For example, engagement of CD40 on endothelial cells by activated T cells expressing CD40L leads to upregulation of adhesion molecules such as ICAM-1, VCAM-1, and E-selectin, which results in increased leukocyte margination (47, 67). Activation of APC by CD40-CD40L interaction induces the production of inflammatory cytokines, chemokines, NO, and metalloproteinases. Interaction of $CD4^+$ $CD40L^+$ T cells with CD40 on B cells leads to B-cell differentiation, proliferation, immunoglobulin (Ig) isotype switching, and formation of memory B cells. The physiological function of CD40L is underscored in patients with congenital deficiencies of the CD40L gene. This X-linked inherited immunodeficiency, the hyper-IgM syndrome, is characterized by the absence of mature antibody isotypes and persistence of high titers of circulating IgM, confirming that the interaction between CD40 on B cells and CD40L on activated T cells is crucial for Ig isotype switching (1).

REGULATION OF CD40L EXPRESSION

CD40L expression is normally tightly regulated. TCR ligation initiates the induction of CD40L expression on the surface of the activated T cells. Additional costimulatory or cytokine signals enhance CD40L upregulation. CD40L mRNA expression peaks 1 to 2 h after T-cell stimulation, and cell surface CD40L protein is fully expressed within 4 to 6 h. Rapid disappearance from the cell surface follows, as CD40L is barely detectable by 16 h (18). This transient CD40L expression gives the antigen-activated T cell a brief opportunity to deliver helper signals to interacting B cells, macrophages, or dendritic cells. Other cell surface accessory molecules have been found to help CD40L expression, including CD28, LFA-3, and ICOS (11, 44, 59). Specific cytokines, such as IL-2, IL-12, and IL-15,

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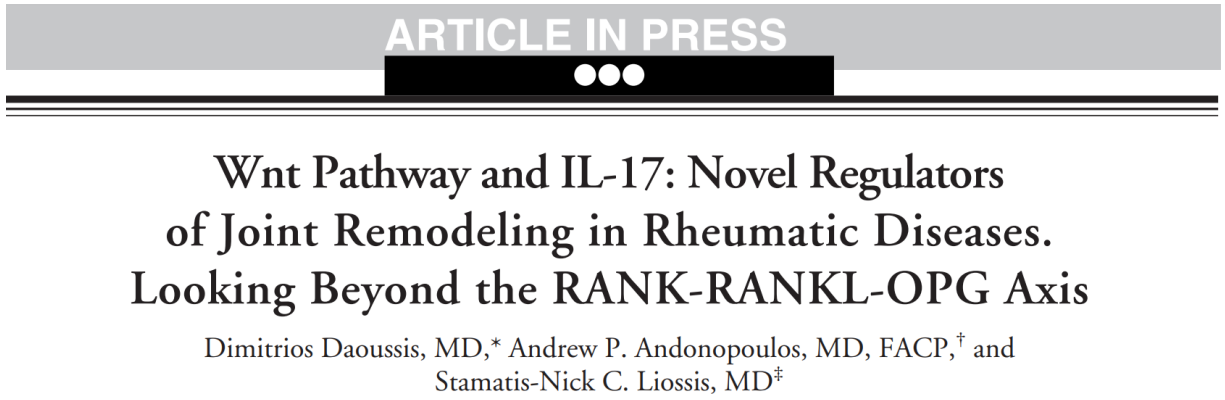
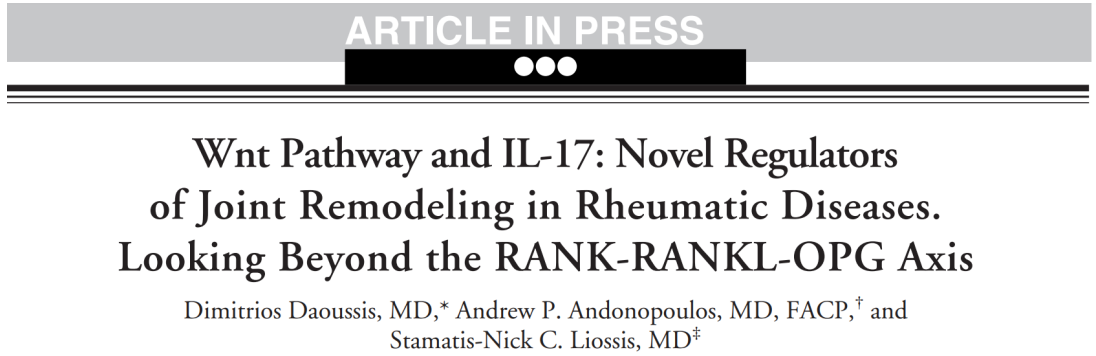
Next attempts….

- The revision process….



Title revision…..
The title is far more important than one realizes….

- **Novel regulators of joint remodeling in rheumatic diseases. Looking beyond the RANK-RANKL-OPG axis.**


ARTICLE IN PRESS

Wnt Pathway and IL-17: Novel Regulators of Joint Remodeling in Rheumatic Diseases. Looking Beyond the RANK-RANKL-OPG Axis

Dimitrios Daoussis, MD,* Andrew P. Andonopoulos, MD, FACP,† and Stamatis-Nick C. Liossis, MD‡

Rev#1: The title does not convey the subject discussed in the review. Possibly Wnt and IL-17 should be explicitly included in the title, something like: "....looking beyond the RANK-RANKL-OPG axis to Wnt and IL-17..."

Rev#2:Title should include Wnt and IL-17, which will help readers to know what this review covers from reading the title. Suggested title is "Wnt signaling and IL-17, novel regulators of joint remodeling in rheumatic diseases, Looking beyond the RANK-RANKL-OPG axis".

As is, the abstract is of little value. The Methods, Results and Conclusions section should be expanded as they provide little information.

Original

- Abstract
- **Objectives-Purpose of review:** During the last decade research has focused on the RANK-RANKL-OPG pathway, that is currently considered the final common route to bone and joint remodeling. The potential role of novel additional mediators has been highlighted by several reports. This review focuses on the recent information about the pathophysiology of the Wnt pathway and IL-17, in relation of their role in bone and joint remodeling
- **Methods:** Extensive internet search was performed (Pub Med) using several keywords.
- **Results/Conclusions:** The available data suggest that mediators in these two biologic systems are critical in joint remodeling and may be appropriate targets in the treatment of bone and joint abnormalities that characterize a variety of inflammatory arthritides and bone diseases.

Revised

- **Objectives:** During the last decade research has focused on the RANK-RANKL-OPG (Receptor Activator of Nuclear factor KappaB- Receptor Activator of Nuclear factor KappaB Ligand- Osteoprotegerin) pathway, that is currently considered the final common route to bone and joint remodeling. The potential role of novel additional mediators has been highlighted by several reports. This review focuses on the recent information about the pathophysiology of the Wnt pathway and interleukin-17 (IL-17), in relation of their role in bone and joint remodeling.
- **Methods:** Extensive internet search was performed (Pub Med) from 1998 and onwards using the following keywords: Wnt, bone remodeling, bone, rheumatic diseases, rheumatoid arthritis, IL-17, Th17, osteoblastogenesis and osteoclastogenesis.
- **Results:** Several members of the Wingless (Wnt) pathway play an important role in bone remodeling. Recent experimental data indicate a key role for Dickkopf-1 (Dkk-1), a soluble inhibitor of the Wnt pathway, in bone remodeling. Increased Dkk-1 levels are linked to bone resorption and decreased levels to new bone formation. LRP5 (low density lipoprotein receptor related protein 5), the main receptor that mediates Wnt signaling, plays a critical role in bone mass regulation. Gain-of-function mutations of LRP5 cause high bone mass (HBM) phenotypes whereas loss-of –function mutations are linked to severe osteoporosis. IL-17 is a proinflammatory cytokine which is produced by a recently described T cell subset, known as Th17 cells. Evidence suggests that IL-17 is a critical mediator of joint destruction in animal models of arthritis. IL-17 blockade has beneficial effects on murine arthritis, a fact that points to the direction of this cytokine as a potential therapeutic target in human inflammatory artritides as well.
- **Conclusions**: The available data suggest that mediators in these two biologic systems are critical in joint remodeling and may be appropriate targets in the treatment of bone and joint abnormalities that characterize a variety of inflammatory arthritides and bone diseases.

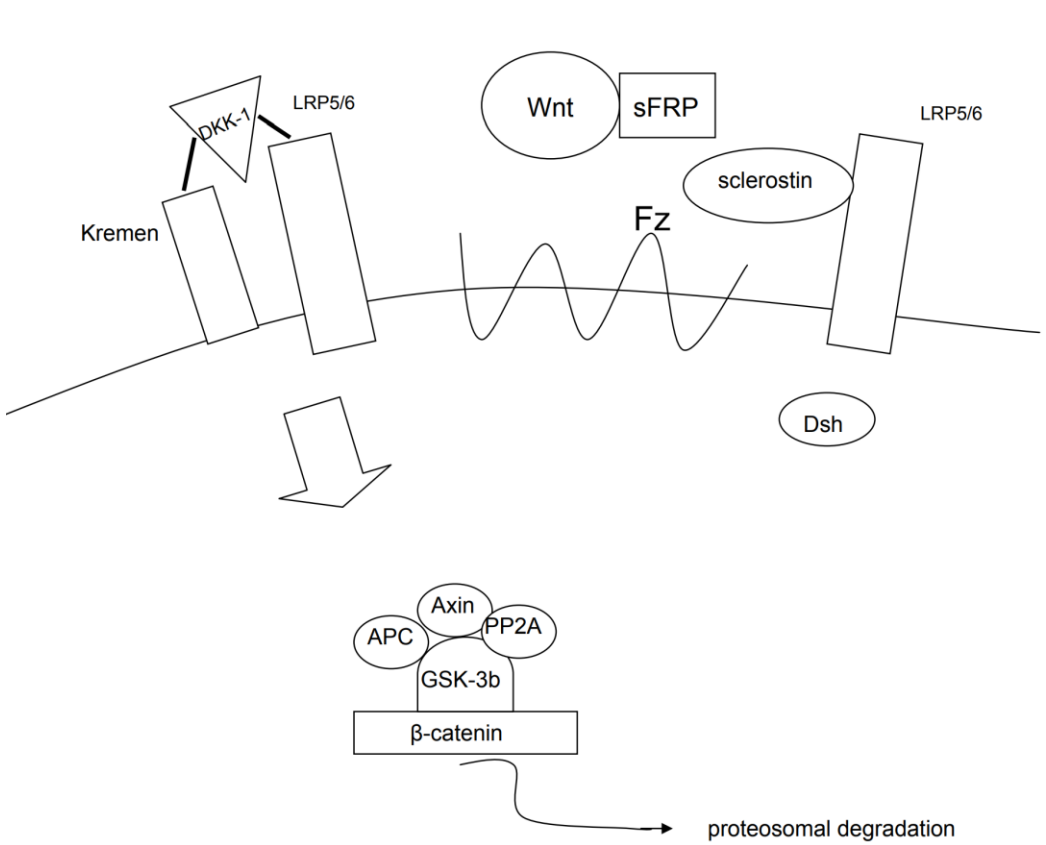
Reviewer comments

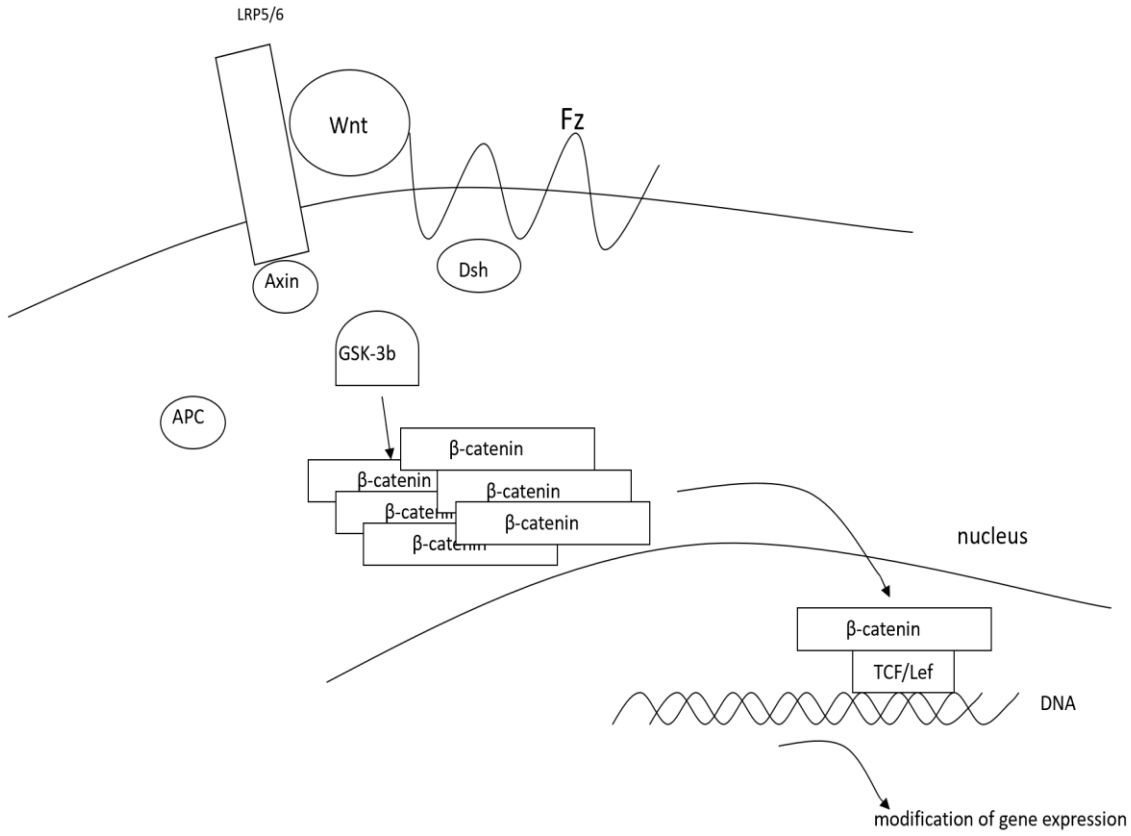
- **ALL abbreviations should be defined on first usage, both in the abstract and in the text, and used consistently thereafter. Once used, do not redefine a second or third time.**

- **Suggest shortening the paper by 10-15% if possible to make it more reader friendly.**

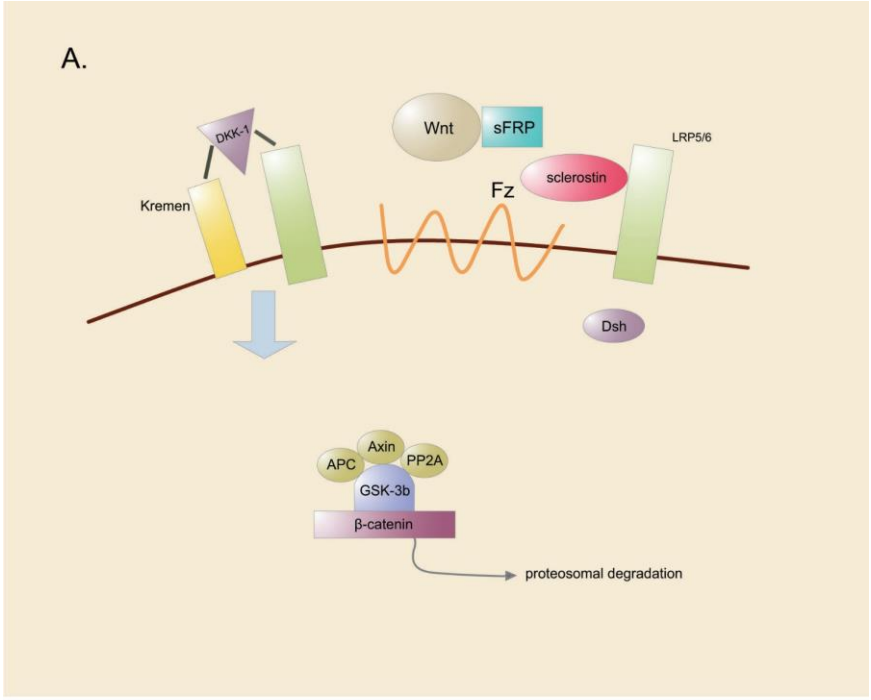
- **The figure is of poor quality and will not reproduce well. It should be redone professionally.**

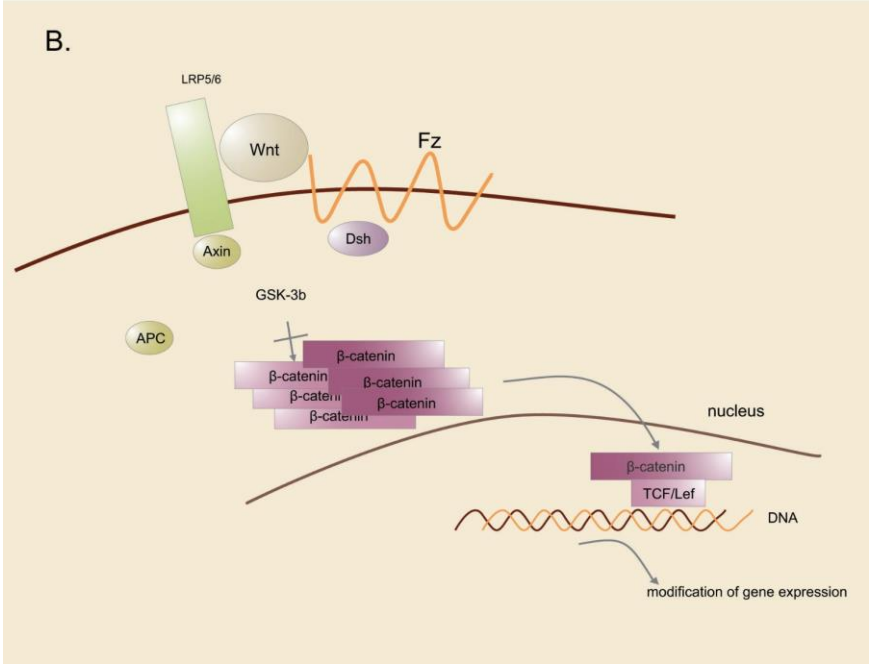
Initial figures



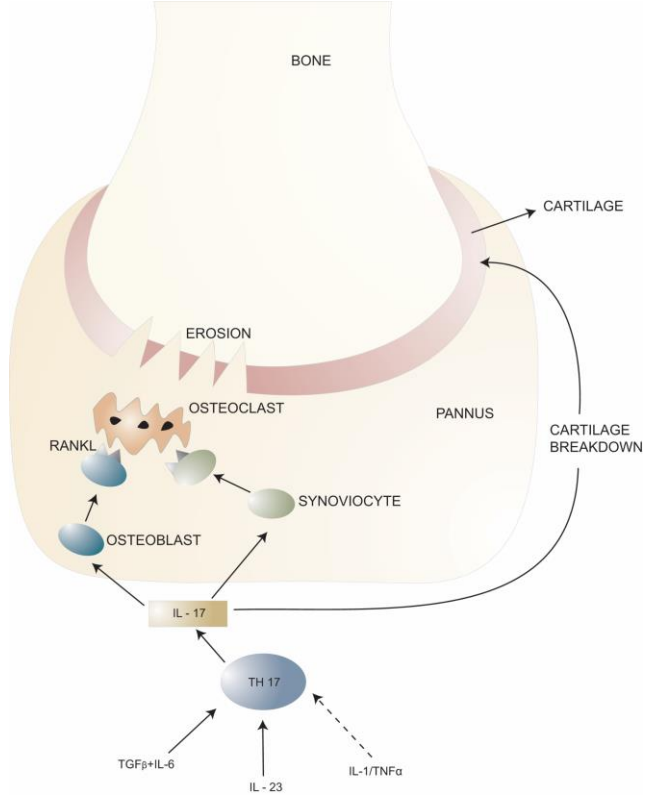


The quality of the Figure, at least in the version of the pdf I downloaded was extremely poor. This may be a technical problem





Revised figures
Figures are a crucial visual aid



It will be greatly helpful if the authors include a figure describing how **the th17 cells produce IL-17 in response to cytokines in inflammatory pannus and affects osteoclast formation indirectly through the up-regulation of RANKL production by synovial cells and osteoblasts.**

- **Major:**
  1. Some more information about the exact methodology used for the literature review. How systematic was this? Why only PubMed was searched? What were the exact Mesh terms used? Were any standardised quality criteria used for the selection of the final 110 references included in the article and the exclusion of others?
- **Reply**
- We do acknowledge that the Methods section of the initial manuscript provided only minimum information- this was done in order to keep the size of the article as short as possible. We agree though that some more information should be provided. We have fully reconstructed the Methods section in the revised manuscript in order to answer the questions raised. Our search was focused on PubMed since the amount of information retrieved from that database only was enormous. It is certainly difficult to apply standardised quality criteria in basic research studies – something that can be done much more easily in clinical studies. Studies were selected based on relevance to study subject and scientific interest.

- No Methods in the initial manuscript!!!!

Revised form

We carried out an extensive internet search (PubMed) from 1998 and onwards. We searched in scientific journals and congress conference proceedings. The computerized searched was completed with a manual search of reference lists from the articles retrieved. The keywords used were: Wnt, bone remodeling, bone, rheumatic diseases, rheumatoid arthritis, IL-17, Th17, osteoblastogenesis and osteoclastogenesis.

- **Isn't there a way to make the tables less "verbose"?**

- In this review we had to organize and present a huge amount of information. The tables were constructed in order to provide significant amount of data without increasing the total size of the manuscript. We do acknowledge though this issue and in the revised manuscript we have omitted some data from the tables in order to make them more reader-friendly

Biologic functions of the Wnt pathway regarding bone metabolism/remodelling	
Mesenchymal cell differentiation	It has been shown that β-catenin signaling is essential in determining whether mesenchymal progenitors become osteoblasts or chondrocytes(92;93). Recent evidence also suggests that Wnt/β-catenin signaling in mesenhymal precursors represses adipogenesis, by inhibiting adipogenic transcription factors, and stimulates osteoblastogenesis, thus favoring new bone formation(94-97).
Cancer a)Multiple myeloma b)Metastatic bone disease	The Wnt pathway is a key player in multiple myeloma (MM) bone disease (98). Newly diagnosed MM patients exhibit increased Dkk-1 serum levels, which correlate positively with the extent of osteolytic bone disease (99). Dkk-1 overexpression in MM has been attributed to persistent activation of the JNK pathway (100). Antibody-based inhibition of Dkk-1 in SCID mice engrafted with MM cells led to an increase of BMD compared to pretreatment levels. Histologic examination revealed that this therapy also led to osteoclast reduction and reduced MM disease burden, indicating a potential beneficial role of this form of therapy in MM (101). The Wnt pathway has been implicated in the establishment of osteoblastic metastasis. Prostate cancer cells exhibit increased Wnt signaling which may explain the osteoblastic nature of prostate cancer metastases (102). Cancer cells appear to produce Dkk-1 early in the development of skeletal metastases which favors an osteolytic environment at the metastatic site. Dkk-1 expression is critical in determining the osteoblastic or osteolytic nature of metastatic disease (103).
Steroid-induced osteoporosis	Steroids suppress Wnt/β-catenin signaling by enhancing expression of Dkk-1 and SFRP-1 and activating GSK-3β (104-106).
Bone mass regulation-Osteoporosis	The Wnt pathway is critical in terms of bone mass regulation, making it an appealing target for the treatment of osteoporosis (107;108). The most attractive targets in order to activate the Wnt/β-catenin pathway are probably the bone specific inhibitors sclerostin and Dkk-1 (101;109). Their tissue specificity is their major advantage and blocking them will probably lead to bone specific results without systemic side effects. Those treatments are currently under development.
Bone response to mechanical loading	Activation of the Wnt/β-catenin pathway seems to be the normal physiological response to mechanical loading (110). There is also evidence that mechanical loading decreases sclerostin expression thus locally relieving Wnt inhibition and activating bone formation (111).

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- In several cases in the review authors describe in detail other investigators' findings and devote a whole paragraph just to repeat the main findings of other researchers. In a comprehensive review as that they should rather report briefly but consistently the other investigators' results and then devote more sentences in an effort to INCORPORATE the findings into the general context of the discussed topic and DISCUSS and COMPARE these findings with established literature data.

- This is a very intertesting review of the potential role of the Wnt pathway and IL-17 in bone remodelling. The field is of interest to basic scientists, clinical scientists and (eventually) to clinicians, and the authors try to engage these audiences, and mostly achieve to do so. The review is well structured. The standardised way of presenting the data for each molecule as they arise from animal models, human systems and different disease states works well. In places there appears to **be a bit too much attention to the detail of experimental design and findings**, and a bit less attention to the concept, mechanism or potential application of the work, but the concluding remarks make up for that to a large extent.

- **Too much “technical” details are unnecessary. The reader can always refer to the primary source if interested in technical details**

- Editor:This worthwhile review should be accepted for publication after suitable revision.
- Rev #1:This is a very intertesting review of the potential role of the Wnt pathway and IL-17 in bone remodelling. The field is of interest to basic scientists, clinical scientists and (eventually) to clinicians, and the authors try to engage these audiences, and mostly achieve to do so. The review is well structured. The standardised way of presenting the data for each molecule as they arise from animal models, human systems and different disease states works well.
  Rev#2:This manuscript covers the recent progress on the involvement of Wnt signal molecules and IL-17 in rheumatism. The literature research is extensive and the content will benefit both basic scientists and clinicians in arthritis filed. The paper is well written and presented. No major concerns.
- Rev#3: This is a very well written comprehensive review on regulators of bone and joint remodeling in rheumatic diseases beyond the well described RANKL/OPG axis. The structure is correct, the bibliographic references exhaustive, the discussion and comments adequate and the analysis complete. I suggest that it should be accepted with minor revision. The following comments are minor: