Dr. Mohan R. Wani

Details of the research work duly signed by the applicant, for which the Sun Pharma Science Foundation Research Award is claimed, including references and illustrations (not to exceed 6000 words).

Area of specialization: Pathophysiology of bone and cartilage remodeling in musculaoskeletal and autoimmune diseases such as osteoporosis, osteoarthritis and rheumatoid arthritis. *Stem Cell Biology and Regenerative Medicine.*

Dr. Mohan Wani is doing both basic and translational research to understand the pathophysiology of bone and cartilage remodeling in context with osteoporosis, osteoarthritis and rheumatoid arthritis (RA). He has made outstanding contributions in identifying the novel role of IL-3 in preventing pathological bone and cartilage loss in musculoskeletal and autoimmune diseases. He also demonstrated the stimulatory role of IL-3 on bone formation. His novel findings strongly suggest the therapeutic potential of IL-3 in important skeletal and autoimmune diseases. He has done original, very focused and goal-oriented research, which is summarized below in 4 sections.

A) IL-3 prevent pathological bone loss

Bone contains two distinct cell types, osteoblasts, essential for bone formation; and osteoclasts, essential for bone resorption (break-down). Co-ordinated activity of osteoblasts and osteoclasts is essential to maintain bone homeostasis and structural integrity of skeleton. Increased osteoclast activity and simultaneous decrease in osteoblast function result in pathological bone loss in musculoskeletal and autoimmune diseases. The present treatment prevents only the partial bone loss and does not induce new bone formation. Mohan Wani investigated the novel role of IL-3 in regulation of pathological bone loss and obtained following important research leads.

- He revealed that IL-3 acts directly on mouse osteoclast precursors, and inhibits receptor activator of NF-κB ligand (RANKL)-induced osteoclast differentiation and diverts the cells to macrophage lineage *(Khapli et al. 2003, The Journal of Immunology).*
- TNF-α is crucial to the pathogenesis of osteoporosis and RA. Further, he demonstrated that IL-3 inhibits TNF-α-induced osteoclast differentiation by inhibiting the expression of TNF receptors *(Yogesha et al., 2005, Journal of Biological Chemistry*).
- IL-3 also inhibits the TNF-α-induced bone resorption in presence of many pro-inflammatory cytokines such as IL-1α, TGF-β_1, TGF-β_3, IL-6 and PGE_2. Interestingly, IL-3 prevents the development of inflammatory arthritis in mice, and protects cartilage and bone destruction *(Yogesha et*

al, 2009, The Journal of Immunology). These novel findings are highlighted by ***Nature Reviews Rheumatology 2009.***

- This study was further extended to human osteoclast differentiation. Interestingly, IL-3 also inhibits human osteoclast differentiation and diverts the cells to dendritic cell lineage. Moreover, IL-3 inhibits bone resorption in osteoclast precursors of osteoporotic individuals *(Gupta et al., 2010 The Journal of Immunology).*

- Importantly, IL-3 helps in restoring decreased RANKL/OPG (osteoprotegerin) ratio in mice, which is observed in important skeletal disorders *(Singh et al., 2018, The Journal of Immunology).*

B) IL-3 has important immunomodulatory role in rheumatoid arthritis

- In mouse model of RA, he demonstrated that IL-3 attenuates collagen-induced arthritis (CIA) by modulating the development of regulatory T (Treg) cells and production of pro- and anti-inflammatory cytokines in mice (Srivastava et al., 2011, *The Journal of Immunology*).

- IL-3 inhibits the development of pathogenic Th17 cells and increases the number of Treg cells in IL-2-dependent manner and ameliorates CIA in mouse model of human RA *(The Journal of Immunology- revised manuscript submitted).*

- He further investigated that the expression of IL-3R on T helper cells is modulated by IL-4; and IL-3 regulates the development and effector function of Th2 cells *(Kumar et al., 2020, The Journal of Immunology).*

C) Tissue regenerative potential of IL-3

- In osteoporosis and RA, the osteoblast number is decreased and they are defective in synthesis of bone matrix. He found that IL-3 increases osteoblast differentiation and mineralization from human mesenchymal stem cells (MSCs) in both in vitro and in vivo conditions *(Barhanpurkar et al., 2012, Biochem Biophys Res Commun).*

- Regeneration of bone requires recruitment of MSCs with increased potential for osteoblast differentiation. Interestingly, IL-3 enhances in vivo migration and wound healing abilities of MSCs *(Barhanpurkar-Naik et al. 2017 Stem Cell Research and Therapy).*

- He further demonstrated that IL-3 ameliorate degeneration of articular cartilage and subchondral bone in osteoarthritic mice, and also prevent degeneration of human cartilage (*Kour et al., 2016 The Journal of Immunology).* These findings are highlighted by **Nature Reviews Rheumatology, 2016**).

D) Stem cell applications in regenerative medicine

- He has developed adult MSCs lines from bone marrow and adipose tissues of mice and human. He found that adipose tissue-derived MSCs prevent pathological bone loss, suppresses autoimmune T cell responses and promote immune tolerance by increasing the percentages of peripheral regulatory T and B cells in mice (Garimella et al., 2015, The Journal of Immunology).

Overall, Dr. Wani's research leads strongly suggest the potential of IL-3 to prevent pathological bone and cartilage loss in important diseases of clinical importance such as osteoporosis, osteoarthritis and RA. His novel research work has featured in several high impact international journals and patents; and highlighted twice by Nature Reviews Rheumatology. His work is also recognized by three National Science Academies including National Academy of Medical Sciences (NAMS), Indian National Science Academy (INSA) and The National Academy of Sciences, India (NASI).

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