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Alpha-2 Macroglobulin in the Management of Chronic and Neuropathic Pain: Synergistic Roles of Exosomes, Mesenchymal Stem Cells, and a Comparative Perspective with Platelet-Rich Plasma Therapy**Jeimylo C. de Castro**

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Chronic and neuropathic pain syndromes remain among the most challenging conditions to treat, often resulting in long-term disability and diminished quality of life. Traditional regenerative therapies such as Platelet-Rich Plasma (PRP) have offered promising results, yet emerging biotechnologies point toward more advanced and mechanistically comprehensive interventions. This presentation explores the therapeutic potential of alpha-2 macroglobulin (A2M) as a master protease inhibitor with anti-inflammatory properties, and its synergistic interaction with exosomes and mesenchymal stem cells (MSCs), specifically adipose-derived (ADSCs) and bone marrow-derived stem cells (BMSCs). A2M functions by trapping pro-inflammatory cytokines and catabolic proteases, directly modulating the biochemical environment implicated in cartilage degradation and neural sensitization. When combined with exosomes, nano-vesicles rich in anti-inflammatory cytokines, miRNAs, and growth factors, A2M's bioactivity is further amplified through paracrine signaling pathways. Moreover, MSCs, particularly those derived from adipose tissue and bone marrow, provide immunomodulatory and trophic support, facilitating neuroregeneration, tissue repair, and pain resolution at a cellular level. Clinical and preclinical data suggest that these therapies offer superior outcomes in both pain reduction and tissue restoration compared to PRP. While PRP mainly delivers

autologous growth factors and cytokines, it lacks the targeted protease inhibition of A2M and the regenerative signaling capacities of stem cell-derived exosomes. Furthermore, MSCs can differentiate into neural, cartilage, and connective tissue lineages, providing a more comprehensive regenerative approach. This multi-modal strategy, leveraging A2M for enzymatic control, exosomes for intercellular communication, and MSCs for tissue regeneration, represents a paradigm shift in the treatment of refractory pain conditions. It surpasses PRP in efficacy, durability of response, and mechanistic coverage. This presentation will detail the molecular biology, therapeutic mechanisms, and clinical evidence supporting the integration of these biologics and propose a future roadmap for personalized pain management strategies utilizing next-generation regenerative medicine platforms.

Biography

Jeimylo C. de Castro, MD, FPARM, RMSK, DABRM, CIPS is the Medical Director and CEO of SMARTMD, Philippines. He is a board-certified specialist in Physical Medicine and Rehabilitation with expertise in sports medicine, musculoskeletal ultrasound, interventional pain management, and regenerative rehabilitation. Dr. de Castro is an internationally recognized speaker, researcher, and author, with numerous scientific publications and book chapters. He is committed to advancing evidence-based, non-surgical therapies that improve patient outcomes and quality of life.