RE-PROGRAMMING THE INFLAMMATORY MICROENVIRONMENT OF THE SYNOVIAL JOINT IN OSTEOARTHRITIS WITH CELL THERAPY – A CONCISE UPDATE ON TISSUE-GENE-C

REPROGRAMIRANJE INFLAMATORNOG MIKROOKRUŽENJA U SINOVIJALNIM ZGLOBOVIMA SA OSTEOARTRITISOM POMOĆU ĆELIJSKE TERAPIJE – SAŽET PREGLED TISSUEGENE-C

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Editorial
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Osteoarthritis (OA) remains the most prevalent chronic joint disease globally [1], characterized by progressive articular cartilage degeneration, synovial inflammation, and debilitating pain [2,3]. Despite its profound socioeconomic impact, therapeutic strategies have historically remained limited to symptom management, such as non-steroidal anti-inflammatory drugs (NSAIDs) and, eventually, total joint replacement [4,5]. The current medical landscape urgently demands disease-modifying therapies that can halt progression, repair tissue, and address the multifaceted pathology of OA, which is now understood to be a complex mechano-inflammatory disease [6,7].

The convergence of cell biology and gene engineering is heralding a critical new era of therapeutic development for OA, exemplified by advanced therapies designed to fundamentally re-program the intra-articular microenvironment [8,12]. The next generation of OA treatment is centered on utilizing sophisticated biological agents to intervene at the molecular and cellular level. Among the most promising of these is TissueGene-C (TG-C), an allogeneic cell and gene therapy product **(Figure 1)** [13].

TG-C comprises a mixture of human allogeneic chondrocytes and a population of irradiated, genetically modified cells engineered to overexpress trans-

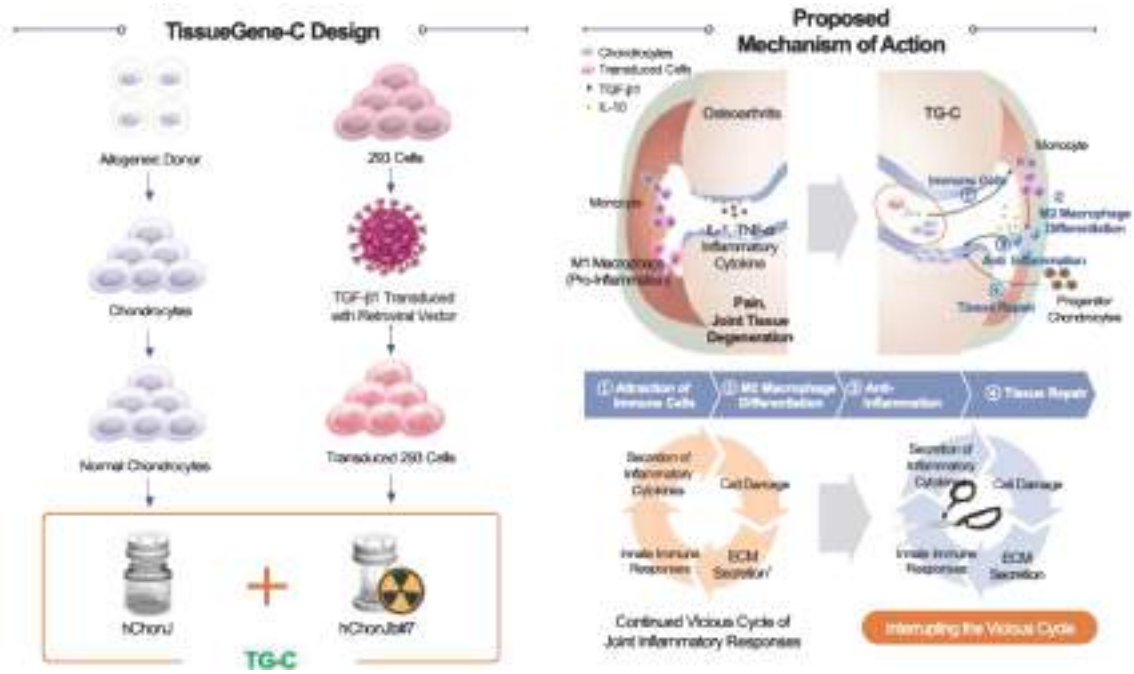

Figure 1. Design and mode of action of TissueGene-C

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forming growth factor beta 1 (TGF-b1) [14]. This dual-component approach is designed to deliver a potent therapeutic protein directly to the diseased joint, effectively turning the administered cells into localized "cellular factories" for TGF-b1 signalling. The action mechanism of TG-C is highly multimodal, targeting both the inflammatory and painful aspects of the disease. Major focus is the modulation of the synovial inflammation [15–17]. In OA, the innate immune system plays a key role and the joint capsule is often infiltrated by pro-inflammatory M1 macrophages [18–21]. Studies demonstrate that TG-C actively induces an anti-inflammatory microenvironment through the polarization of M1 macrophages towards the M2 phenotype [22]. The M2 macrophage is crucial for tissue repair and inflammation resolution, releasing anti-inflammatory cytokines and growth factors [23,24]. This shift is critically mediated by the activation of the prostaglandin E2 (PGE2) signalling pathway [25]. By boosting PGE2 activity, TG-C utilizes a powerful endogenous mechanism to resolve inflammation and promote an environment conducive to cartilage structural improvement [26]. Beyond its role in immunomodulation and structural repair, TG-C exhibits promising potential in long-term pain management [22]. OA-related pain is not merely a consequence of mechanical wear but is driven by biochemical mediators and the sensitization of peripheral sensory neurons. The research that we have done thus far indicates that TG-C induces long-term analgesic effects by directly regulating pain mediators within the joint [22]. By counteracting the effects of molecules that induce neuronal sensitization (e.g., in the dorsal root ganglion), this therapy effectively dampens the hyper-responsive state of the nerve fibres. This neurobiological effect is key to addressing the neuropathic-like component of OA pain, providing relief that is often durable and goes beyond simple chondroprotection.

The development of such advanced regenerative therapies is linked to advancements in protein production technologies. The feasibility of producing therapeutic proteins like TGF- b1 at clinical scale relies on sophisticated platforms utilizing mammalian cell lines [14,27]. These "protein production platforms," including the use of irradiated and transfected cells, are essential for ensuring the reliable and high-yield over-production of therapeutic growth factors necessary for clinical application.

In summary, cell and gene therapies, particularly those utilizing engineered cells to express potent growth factors like TG-C, represent a unique and transformative approach to OA therapy. By simultaneously resolving inflammation through M2 macrophage polarization, promoting structural repair, and reversing neuronal sensitization, these therapies offer the prospect of disease modification. For the osteoarthritis research community, the imperative is clear: we need to integrate these technical advances into translational and clinical studies and currently a Phase II clinical study of TG-C is underway, with results expected in 2026. The ongoing clinical trial of TG-C involved rigorous assessment of pain and function, and joint preservation. If successful, TG-C will become the first approved cell therapy for OA.

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