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Strategic routes for 3d printing of engineered meniscal substitutes

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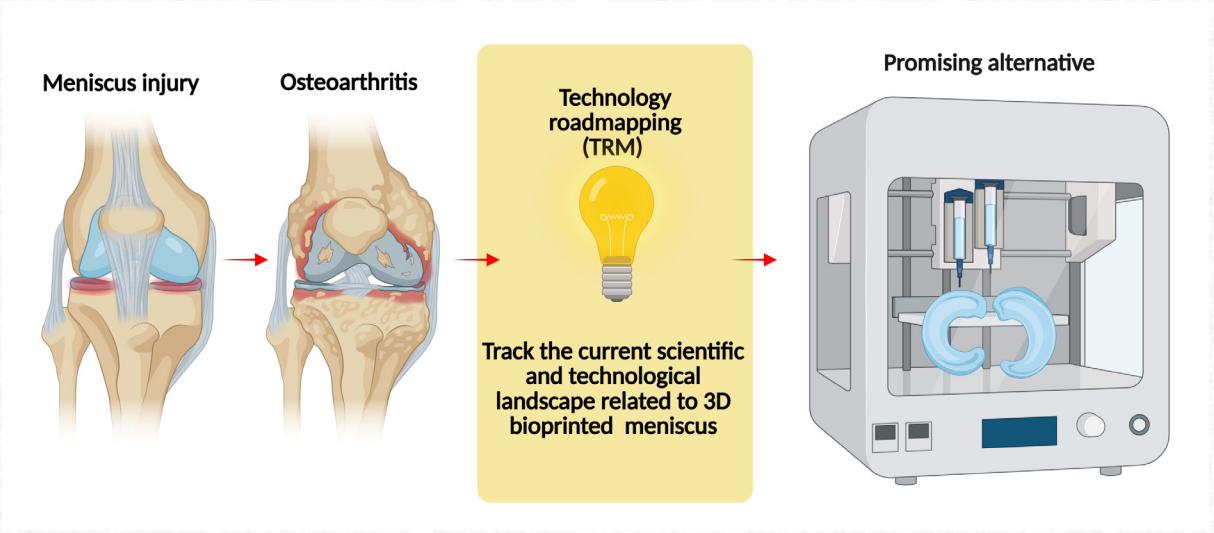

Abstract: Complex meniscal injuries represent a significant clinical challenge due to their high prevalence and limited regenerative capacity. Conventional surgical approaches, such as meniscectomies, often yield unsatisfactory therapeutic outcomes, leading to mid- to long-term osteoarthritis. In this context, 3D-printed engineered meniscus substitutes (PEMS) emerge as a promising alternative to mitigate these disabling complications. To map the scientific and technological landscape of PEMS development, a rigorous bibliometric analysis was conducted across ScienceDirect, PubMed, and Web of Science (2015–2023). The search strategy combined the terms: "meniscus" AND "scaffold" AND "3D bioprinting" AND "tissue engineering" AND "regenerative medicine" AND "biomaterials". After screening and duplicate removal, 15 articles were selected from 128 initially identified. Exclusion criteria included reviews, studies lacking 3D bioprinting in meniscal scaffolds, unrelated tissue research, and purely computational analyses. Key technological parameters—biomaterials, printing processes, and cells/biomolecules—were extracted from the selected articles. These findings informed the creation of a Technological Roadmap (TRM) to outline current tissue engineering strategies for PEMS, identifying technological trends, knowledge gaps, and emerging opportunities. The proposed TRM offers a structured framework to foster interdisciplinary collaboration, prioritize research efforts, and accelerate the development of clinically viable PEMS.

Keywords: Meniscus. Bioprinting. Tissue Engineering. Roadmap.

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Introduction

The rapid pace of technological evolution driven by market demand has directly impacted project planning and development by research groups[1]. The push for innovation has forced companies and researchers to use technological planning and management tools, providing decision-makers with insights into the directions and trends new technologies should follow, aligned with market and competitor interests[2,3]. As a result, researchers face dilemmas between the need for concrete information and the overwhelming volume of accessible data, creating knowledge gaps that hinder progress and delay the resolution of technological challenges [4].

In this context, technology prospecting methods have emerged as valuable tools to address this demand, utilizing approaches like Technology Roadmapping (TRM). TRM aims to align technological strategy drivers (research gaps, trends, products, and market) with the development of innovative products offering greater market potential[5-6]. It is a powerful technique for supporting technology management and planning[7], particularly in exploring and communicating the dynamic connections between technological resources, organizational goals, and external environmental changes[8-10].

Meniscal injuries represent a critical medical challenge, driven by their high prevalence, inherently limited regenerative capacity, and the unsatisfactory outcomes of conventional treatments [11]. Surgical interventions such as meniscectomies are structurally incapable of restoring long-term joint functionality, as the removal of meniscal tissue eliminates its shock-absorbing role, leading to progressive joint overload, inevitably accelerates cartilage degeneration, culminating in debilitating osteoarthritis[12]. The cascade of complications not only compromises patient quality of life but also imposes significant socioeconomic costs, including prolonged healthcare expenses and lost productivity [13]. These systemic challenges underscore the urgent need for innovative therapeutic strategies that fully restore meniscal biomechanics and biological function, preventing further joint degeneration[14]. One promising alternative is the development of 3D printed engineered meniscus substitutes (PEMS) through tissue engineering (TE) and 3D bioprinting [15,16]. 3D bioprinting was prioritized in this study due to its unique capacity to fabricate complex, patient-specific architectures with precise spatial control over cells and biomaterials, critical for replicating the meniscus's heterogeneous structure. However, the meniscus's complex anatomical structure and the biomechanical limitations of available materials necessitate parallel technological advancements to achieve biomimetic accuracy in 3D construction[17,18]. This challenge requires integrating multidisciplinary knowledge, each demanding technological progress, while managing the risks of incompatible or trade-off solutions. This complex scenario generates numerous technological pathways, complicating the definition of a clear development strategy.

The challenges in developing PEMS are typical of most technological innovation processes in medicine and healthcare, both of which have benefited from the use of TRM[19-22]. However, no prior efforts have applied TRM specifically to PEMS. Therefore, this study aims to create a TRM to track the current scientific and technological landscape related to tissue engineering strategies for PEMS.

Materials and methods

Mapping and analysis of scientific and technological publication

For the mapping of scientific and technological approaches related to engineered meniscal substitutes (PEMS), the ScienceDirect, PubMed, and Web of Science databases were selected. Two search strategies were employed: "meniscus" AND "scaffold" AND "3D bioprinting" AND "tissue engineering" and "meniscus" AND "scaffold" AND "3D bioprinting" AND "tissue engineering" AND "regenerative medicine" AND "biomaterials". The search was limited to original scientific articles published between January 2015 and April 2023, and, after removing duplicates across databases, 128 articles were identified. During the preliminary screening phase, 113 articles were excluded for not meeting eligibility criteria aligned with the core scope of this work. Among the reasons for exclusion were review articles, studies that did not address 3D bioprinting techniques in the fabrication of meniscal scaffolds, research focused on other articular tissues (e.g., hyaline cartilage) without direct relevance to meniscal regeneration, and exclusively computational studies. The remaining 15 articles were thoroughly analyzed to identify and characterize technologies suitable for integration into the PEMS proposal, with a focus on parameters such as biomaterials, printing processes, and cells and biomolecules utilized.

Elaboration of TRM

A planning session was conducted before starting the map elaboration[21-24]. During this session, researchers analyzed and categorized information about proposed solutions and technologies, enabling the integration of technologies and highlighting the multidisciplinary nature of the PEMS challenge. The subsequent session focused on consolidating the information relevant to PEMS and validating it. Researchers also identified key knowledge gaps

and specialized information needed to address these gaps. Following this, the content and main messages of the map were considered. The final session completed the process, creating value and insights through the strategic vision provided by the information.

The map was designed with three horizontal layers: the upper layer, "Products," outlines the essential requirements for developing the "printed engineered meniscal substitute"; the intermediate layer, "Technologies," represents the main technologies used by researchers and is divided into four sub-layers: "Biomaterials," "Printing Process," "Cells," and "Biomolecules"; the bottom layer, "Skills," details the crucial skills needed by the research group, as envisioned by the authors, for applying these technologies. The data from the 15 selected articles were organized on the map according to these layers and presented in chronological order.

Results and discussion

Technological prospection map of 3D bioprinting of meniscal substitutes

Figure 1 represents the map generated. In the top layer, "Products," given the absence of a market-ready product, the essential biological and biomechanical requirements for a clinically and commercially viable PEMS were outlined. The analysis of these requirements underscores the critical importance of the biomaterials used in the ink, as they are crucial for achieving desired architecture, biomimicry, mechanical performance, bioactivity, and integration of the development strategies. In the "Technologies" layer, under the "Biomaterials" subcategory, polycaprolactone (PCL) predominated, appearing in 12 of the 15 selected articles, either alone or combined with other materials such as alginate, collagen, poly(lactic-co-glycolic acid) (PLGA), decellularized meniscal extracellular matrix (dmECM), GelMA, polyurethane (PU), carbon nanotubes (CNT), and Tetra-PEG. These materials were chosen for their unique advantages: PCL offers excellent mechanical properties, biodegradability, and ease of processing; alginate provides high biocompatibility and gel-forming capabilities; collagen mimics the natural extracellular matrix, promoting cell adhesion and tissue integration; PLGA combines tunable degradation rates with mechanical strength; dmECM preserves native tissue-specific cues; GelMA enables precise control over hydrogel stiffness and cell encapsulation; PU adds elasticity and durability; CNT enhances mechanical reinforcement and electrical conductivity; and Tetra-PEG allows for highly tunable crosslinking and mechanical properties [25]. However, despite these benefits, most strategies relied on rigid supports, which, although resistant to compressive forces, are technically incompatible with the meniscus's biomechanical environment and joint kinematics. This mismatch highlights a critical limitation, as the meniscus requires materials that can replicate its unique viscoelastic properties and dynamic load-bearing capabilities. The use of rigid materials compromise the functionality and integration of engineered constructs, underscoring the need for more biomimetic approaches that better align with the native tissue's mechanical and biological demands.[26, 27]. The knee joint is a dynamic mechanical environment characterized by multiaxial loads, including compressive, tensile, shear, and torsional forces during movement. However, the meniscus is highly sensitive to mechanical mismatch. Rigid biomaterials, like those often used in current strategies, fail to replicate this viscoelasticity and anisotropy, leading to stress shielding (reducing natural tissue remodeling) or stress concentration at the implant-tissue interface. The knee joint is a dynamic mechanical environment subjected to multiaxial loads, including compressive, tensile, shear, and torsional forces during movement. This biomechanical complexity is counterbalanced by the meniscus's heterogeneous composition, which enables adaptation to cyclic loading while maintaining viscoelastic properties critical for energy dissipation and shape recovery after deformation. However, the meniscus exhibits high sensitivity to mechanical mismatches. Rigid biomaterials, commonly employed in current strategies, fail to adequately replicate its viscoelasticity and anisotropy, leading to stress shielding (which reduces natural tissue remodeling) or stress concentration at the implant-tissue interface. This incompatibility becomes critical, as the meniscus requires materials capable of reproducing not only its unique viscoelastic properties but also its ability to withstand dynamic loads without compromising joint functionality[27].

Under the "Bioprinting Process" subcategory, the extrusion method was predominant, being utilized in 14 studies, while electrospinning was employed in 2 studies, and inkjet printing in only 1 strategy. This significant disparity highlights critical technical factors influencing the selection of printing methods. The dominance of extrusion can be attributed to its versatility, particularly its ability to process high-viscosity bioinks[28, 29], essential for ensuring the structural integrity of load-bearing meniscal substitutes. Furthermore, the scalability of extrusion facilitates the fabrication of large, anatomically precise constructs, a critical factor for clinical translation. In contrast, inkjet printing faces limitations in achieving the mechanical stability required for meniscal substitutes in articular environments, restricting its application[30, 31].

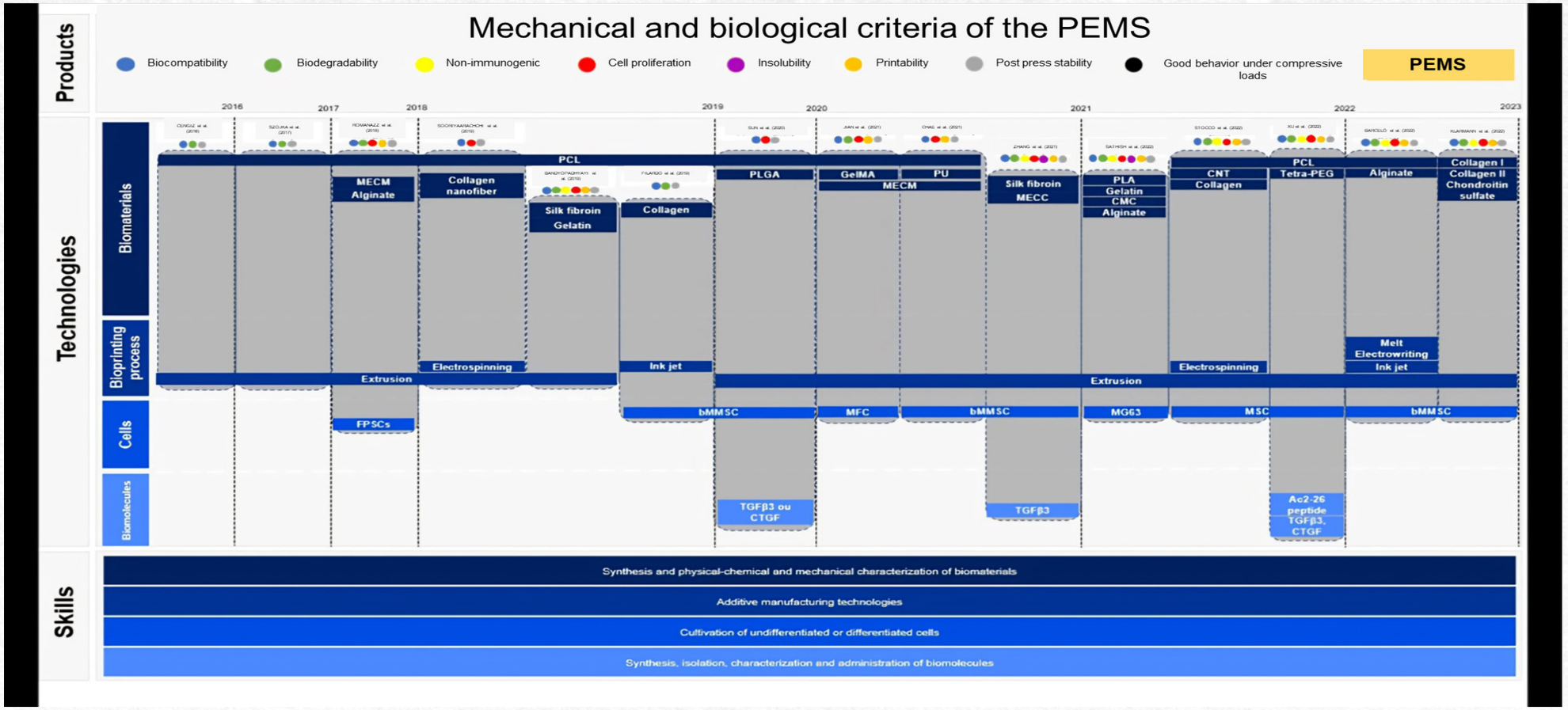

Figure 1 - Technology roadmapping (TRM) for 3D printed engineered meniscus substitutes (PEMS). The TRM integrates three layers to guide PEMS development: Products (Top Layer) - Essential requirements for clinical viability, including biomimetic architecture and biomechanical compatibilit; Technologies (Middle Layer) – Biomaterials, bioprinting process, cells and biomolecules; Skills (Bottom Layer) - Critical competencies (e.g., biomaterial characterization, additive manufacturing) needed to address technological gaps.

A crucial point is that materials compatible with this technology (e.g., low-viscosity hydrogels) may lack the mechanical or structural characteristics necessary for developing functionally viable meniscal substitutes[32]. Electrospinning also presents limitations in this context, particularly in constructing thick, anatomically precise volumetric structures. Although the technique produces nanofibers with a high surface-area-to-volume ratio, promoting cell adhesion, its applicability in meniscal tissue engineering is constrained by the difficulty in depositing controlled three-dimensional layers and its low production rate, which hinders scalability for clinical applications[33].

In the "Cells" subcategory, 11 articles utilized various cell types, including infrapatellar fat pad-derived stem cells, bone marrow mesenchymal stem cells, meniscal fibrocartilage chondrocytes, and osteosarcoma cells. Among these, stem cells stand out as key players, surpassing other cell types in versatility and regenerative potential [34]. Their unique ability for self-renewal, differentiation into multiple lineages, and modulation of the cellular microenvironment makes them essential for innovative approaches in regenerative medicine and tissue engineering, particularly in the context of musculoskeletal regeneration[34, 35]. The use of stem cells in bioinks has gained significant attention due to their unique properties, such as self-renewal, multipotency, and paracrine signaling capabilities. Mesenchymal stem cells (MSCs), for instance, are particularly promising due to their ability to differentiate into various cell lineages, making them ideal for the regeneration of complex tissues [36]. In the specific case of the meniscus, MSCs demonstrate exceptional potential for promoting the repair of this tissue, which plays a critical role in knee biomechanics and is frequently injured in trauma or degenerative processes[37].

In the "Biomolecules" subcategory, only 3 studies manipulated biomolecules, specifically transforming growth factor beta-3 (TGF-β3), connective tissue growth factor (CTGF), and the Ac2-26 peptide. Incorporating biomolecules into bioinks enables the creation of microenvironments that closely mimic the physiological conditions of native tissues, a critical factor in maintaining cell viability and ensuring the functionality of bioprinted constructs[38]. Biomolecules, such as growth factors, cytokines, and extracellular matrix proteins, act as chemical messengers that guide stem cells toward differentiating into specific cell types. This finely tuned signaling not only encourages cellular development but also fosters the formation of more integrated and functional tissues, paving the way for innovative advances in regenerative medicine [39].

In the "Skills" layer, essential skills for developing PEMS were identified as follows: synthesis and physical-chemical and mechanical characterization of biomaterials; additive manufacturing technologies; cultivation of undifferentiated or differentiated cells; and synthesis, isolation, characterization, and administration of biomolecules. Recognizing these skills can help research groups focus on interdisciplinary collaboration to enhance technologies related to the PEMS bioprinting process and advance towards higher levels of technological readiness for achieving a final product[1, 5, 10].

Given this technical and biological complexity, TRM emerges as a strategic framework to harmonize the multiple dimensions involved in the bioprinting of meniscal substitutes. By mapping the identified gaps, TRM enables the prioritization of investments in research lines that address and integrate the highlighted deficiencies. Simultaneously, by emphasizing the need for multidisciplinary skills, TRM can guide the formation of specialized teams and the acquisition of critical infrastructure, bridging the gap between basic research and clinical application. The synergy between TRM and the presented data becomes evident when projecting trajectories to overcome the encountered challenges. Thus, TRM not only consolidates a systemic understanding of current challenges but also transforms fragmented data into a cohesive plan, accelerating technological translation in meniscal tissue engineering.

Conclusions

Strategic planning and technological prospecting tools, such as TRM, are increasingly being utilized in biotechnology to optimize research and product development, particularly in medicine and health. The application of TRM facilitated the creation of a map that presents information on PEMS bioprinting in a chronological, structured, and integrated manner. This map outlines the current state of scientific and technological research related to product requirements. The process that produced the map not only guides researchers and enhances the scientific and technological development process but also supports knowledge management and project direction, essential for advancing towards commercially viable PEMS.

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Competing interests: I have nothing to declare

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