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COMMENTARY

Mesenchymal stem cell membrane-coated nanoconstructs: why have they not yet found a home in clinical practice?

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"for successful clinical translation, creating MSCM-nanoconstructs entails carefully considering several factors, including the construct's features, therapeutic goals, mode of administration, bioavailability, biodistribution, toxicological study, and patient-specific variables"

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A newly developed drug-delivery method involves using cell membranes to encapsulate drug-loaded nanoparticles, creating biomimetic 'nanodecoys' [1,2]. These novel nanoparticulate drug-delivery vehicles have significantly improved the functionality of nano-based approaches by facilitating their efficient movement through the human body and hold much promise for application in diagnostics and medical purposes [3]. To serve effectively in diagnostic applications, nanodecoys can be designed to specifically trap biomolecules, such as proteins, nucleic acids, or small molecules, that act as diagnostic markers for different illnesses. Notably, they may efficiently capture and concentrate target biomarkers from complicated biological samples using specialized binding patterns or ligands. This enables biomarker identification and quantification using analytical methods such as immunoassays or nucleic acid amplification assays [3]. Furthermore, nanodecoys can be engineered to exhibit molecules or ligands on their surface that selectively identify and attach to desired cells or tissues. These targeting moieties consist of antibodies, peptides, or small compounds that exhibit strong affinity and specificity toward receptors or markers found on the surface of the target cells. Notably, viruses, bacteria, toxins, and cancer cells are reported to be captured and neutralized effectively utilizing this strategy [1,2].

During the COVID-19 epidemic, in an animal model i.e., *Cynomolgus Macaques* (three females and three males), nanodecoys derived from human lung spheroid cells exhibited the ability to attach to and neutralize SARS-CoV-2 [2]. Additionally, nanodecoys might be incorporated with active pharmaceutical ingredients or diagnostic tools to increase their therapeutic effectiveness in treating infections or diseases, including cancer. Notably, nanoconstructs and/or nanoparticles that are selectively encapsulated inside mesenchymal stem cells (MSCs) membranes (MSCM) are regarded as groundbreaking in the realms of regenerative medicine and targeted drug delivery [4]. Moreover, the MSCM has been demonstrated to possess inherent capabilities in identifying immune cells and selectively targeting specific tissues, leading to enhanced therapeutic results and less adverse effects in conditions such as osteoarthritis, rheumatoid arthritis, and various malignancies [4]. For example, D'Atri et al. developed a novel kind of MSCM-based nanoparticle, called a nano-ghost (NG) for targeting or treating osteoarthritis [5]. Their investigations suggested that NGs successfully regulated the inflammatory process, specifically in cartilage tissues, and promoted its repair both *in vitro* and *in vivo*. Collectively, their study results demonstrated that the NG system has significant promise as a nanocarrier platform and might serve as an immunomodulatory medication for a broad spectrum of inflammation-related diseases [5]. These observations indicate that MSCM-based nanodecoys have proven therapeutic benefits and remarkable targeting capabilities, but their extensive use in clinical settings is still difficult to achieve. From this perspective, we analyzed the require-

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ments that must be fulfilled to implement these technologies in clinical environments successfully.

Formulation and design are key to producing superior-quality MSCM-nanoconstructs [5,6]. The therapeutic payload encapsulating capability, stability, and precise tissue targeting depend on the properties of the MSCM's surface and the physicochemical characteristics of the nanoconstructs. Applying MSCM in conjunction with nanoparticles offers an excellent solution to the challenges encountered when using either organic or inorganic nanoparticles individually or combined. Inorganic nanoparticles exhibit remarkable stability and unique physicochemical properties. However, they often face challenges such as biocompatibility and potential toxicity, which might limit their utility in biomedicine. Thus, applying MSCM coating to inorganic nanoparticles could significantly enhance their capacity to interact with living organisms without affecting their durability and unique properties and concurrently reducing former toxicity. This approach harnesses the inherent capability of MSCM to develop a bio-hybrid system that combines the advantageous characteristics of both inorganic nanoparticles and MSCs. Conversely, organic nanoparticles such as liposomes, polymeric nanoparticles, and micelles often encounter stability problems due to their tendency to aggregate, rapidly release medicines, degrade, and have a short systemic circulation time. These challenges could substantially restrict their effectiveness in biological applications. The stability and biocompatibility of the former can be significantly improved by coating with MSCM. This bio-hybrid approach utilizes the stability, immune evasion, and targeting characteristics of MSCM to create a nanoparticle system that exhibits enhanced efficacy and prolonged durability for therapeutic administration. Further, it is essential to carefully analyze the formulation features of nanoconstructs, including their size, shape, surface chemistry, and cargo-loading efficiency. This step is necessary to confirm the compatibility of the nanoconstructs with MSCM coating and to maximize their therapeutic benefits [7,8]. Also, customizing or tailoring the MSCM surfaces can make the MSCM coating work even better and keep the therapeutic drug-loaded nanoparticles inside its core in stable form for a prolonged duration. Nevertheless, attaching positively or negatively charged ligands, polymers, or peptides to the surface of the MSCM-nanoconstructs in accordance with the specific cells being targeted can also impart higher zeta potential (positive or negative) and reduce their interaction via electrostatic repulsion. This strategy minimizes the chances of aggregation, prevents off-target effects, and improves stability. However, to effectively do so, nanoconstructs should also mimic MSCM-like properties to elude immune identification, target desired tissues, and modify the immune response [9]. Similarly, by integrating multiple targeting ligands or therapeutic peptides and proteins onto the surface or encapsulated nanoconstructs of an MSCM, its therapeutic potential can be boosted according to the specific properties of the tumor or targeted cells [10,11]. Therefore, while designing multifunctional MSCM-nanoconstructs, we must carefully customize them for biological compatibility, cargo-loading efficiency, and desired synergistic therapeutic benefits. Concurrently, the core nanoparticles and MSCM covering materials should also be biocompatible and biodegradable to reduce the risk of toxicity and overactivity in immune responses. In this regard, natural biomaterials or biocompatible polymers may assure biological empathy and promote bodily clearance [12].

Apart from those above-mentioned challenges, there are a lot of other factors to consider before *in vivo* administration of MSCM-nanoconstructs, such as the dose, the biodistribution mechanism, and most importantly, the characteristics of the target organ or tumor, and the expected therapeutic outcomes [13,14]. Gaining comprehension of these elements facilitates the determination of the appropriate dose and ensures the maintenance of therapeutic consistency. Furthermore, the optimal dosage of MSCM-nanoconstructs may vary depending on the specific use and the patient's medical condition. Researchers often undertake dosage-finding investigations in animal models and human clinical trials to determine the ideal range of doses. Additionally, there are several methods of delivering substances, such as intravenous, intramuscular, intra-articular, intrathecal, and local injection into the specific region [15]. Next, the delivery route is chosen based on factors like disease pathophysiology, desired pharmacokinetic profiling, biodistribution, and safety considerations. Evaluating the biodistribution and pharmacokinetics of MSCM-nanoconstructs is critical for elucidating the appropriate dose and dosing schedule. Research on the dissemination, duration, and elimination of MSC-nanoconstruct structures after administration may aid in determining the appropriate dose and timing of administration [16]. Subsequently, the safety of MSCM-nanoconstructs is evaluated at various dosage levels by dose escalation and toxicological investigations. To ensure the successful progress of preclinical and clinical research, it is of utmost importance to closely monitor and assess any potential side effects, including heightened immune responses, inflammation, and the potential for tumor formation. There is currently a shortage of preclinical research-based data that specifically investigates all these elements of MSCM-nanoconstructs. Therefore, researchers must prioritize fixing these concerns to facilitate the commercialization of nanodecoys and MSCM-nanoconstructs within the next decade.

Next, to improve the stability of MSCM-nanoconstructs, adding hydrophilic coatings on the MSCM surface can increase their durability in water-based settings [17]. In this regard, hydrophilic polymers like polyethylene glycol (PEG) are widely reported to provide steric stabilization, which helps to avoid aggregation and improves colloidal stability [18]. In addition, improving the lipid bilayer structure or fluidity of the MSCM might promote the stability and permeability of nanoconstructs across the desired tissue or cells. Similarly, researchers report that adding lipid stabilizers or incorporating cholesterol into the nanoconstruct enhances membrane integrity and increases their resistance to environmental stresses [19]. Furthermore, incorporating stabilizing chemicals, such as antioxidants or enzyme inhibitors, into the core of nanocomposites protects them from oxidative stress or enzymatic degradation. These strategies can lead to better stability and give them a longer shelf life [20]. Another viable and comparatively less complex method to enhance the stability of MSCM-nanoconstructs during extended storage could be lyophilization. Additionally, this method facilitates the transportation of the former by removing water and also reduces the likelihood of degrading reactions [21]. The stability of MSCM-nanoconstructs can be enhanced throughout the formulation process by using strategies such as maintaining optimal pH levels, temperatures, and ionic strengths. Furthermore, it is crucial to employ rigorous quality control methods to guarantee the stability and uniformity of MSCM-coated nanoconstructs during manufacturing. This requires a comprehensive analysis of the physical and chemical characteristics, as well as performing stability tests under appropriate storage settings [22].

The successful commercialization of nanodecoys or MSCM-nanoconstructs relies on aspects beyond just the cell type and requires relatively simple and reproducible but robust formulation and design, which might be advantageous for their efficient large-scale production and clinical translation. The first step involves designing the nanoparticles *via* the self-assembly method. In this process, nanoparticles autonomously organize into structured patterns or functional architectures without human intervention, driven by specific interactions among the particles and between the particles and their environment, such as Van der Waals forces, electrostatic interaction, hydrogen bonding, hydrophobic interaction and steric effects [1,2]. In addition, formulation scientists could manipulate nanoparticles' form, size, and surface characteristics to imitate desired structures for a specific purpose. Next, to effectively incorporate these self-assembled nanoparticles into the MSCM, simple and scalable methods like extrusion, ultrasound, and electroporation could be employed [1,2]. Moreover, the scale-up production of MSCs is essential to meet the market demand. To scale up for commercial production, bioreactors or cell culture systems are often used in large-scale manufacturing processes to facilitate the proliferation of MSCs by providing controlled environmental variables such as temperature, pH, and oxygen levels. These systems are particularly useful for accommodating higher cell volumes and optimizing cell growth. Furthermore, when assessing clinical translatability, it is critical to examine two key variables thoroughly. One challenge is safety, which may be addressed by employing biocompatible materials that elicit minimal inflammatory and immunological responses, either directly or via their breakdown products. Another concern is efficient and economical manufacturing, which can be addressed using readily available pharmaceutical excipients.

Hence, for successful clinical translation, creating MSCM-nanoconstructs entails carefully considering several factors, including the construct's features, therapeutic goals, mode of administration, bioavailability, biodistribution, toxicological study, and patient-specific variables. By conducting a methodical assessment and optimizing the formulation process, dosage regimens could be carefully adjusted to enhance the effectiveness of therapy using MSCM-nanoconstructs while also prioritizing patient safety in treating various diseases. Moreover, other issues, like regulatory hurdles, manufacturing scalability, and long-term safety, should not be overlooked. Subsequent investigations will indeed focus on the resolution of these obstacles, enhancing the therapeutic efficacy of MSCM-nanoconstructs and broadening their use to include a broader spectrum of disorders. Altogether, the effective use of MSCM-nanoconstructs shows excellent potential for progressing regenerative medicine, cancer treatment, and wound recovery. Ongoing research and collaboration among scientists, physicians, and regulatory agencies are essential to fully harnessing the promise of these novel medicines carriers and making them available to patients in the near future.

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