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MINI REVIEW PAPER

The future prospect of metal-organic frameworks for theranostic purposes in brain disorders

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ABSTRACT

The burgeoning field of nanoscale metal-organic frameworks (NMOFs) has captured substantial attention within the biomedical fields, prompting a shift towards exploring their potential in diagnosis and treating brain disorders. This narrative letter delves into the limited research encompassing NMOF-mediated drug delivery to the brain for neurological conditions compared to other applications. Despite significant strides in diagnosing and treating brain ailments utilizing NMOFs, challenges persist, notably the formidable blood-brain barrier (BBB) hindrance, stability issues, and cost considerations. Enhancing NMOF efficacy requires strategic functionalization, eco-friendly synthesis methodologies, and rigorous toxicity assessments. Overcoming these obstacles involves tailoring NMOF properties for improved BBB penetration and physiochemical stability, alongside meticulous biocompatibility evaluations. To advance NMOF applications in neurological theranostics successfully, concerted efforts towards refining safety, efficiency, precise delivery, and cost-effectiveness are imperative. Addressing these challenges will pave the way for translating this promising technology into practical clinical settings, facilitating enhanced precision and efficacy in neurology.

Keywords: *Brain disorder, Brain disease, Covalent organic framework, Metal-organic frameworks, Theranostics*

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INTRODUCTION

With the growing prevalence of research on nanoscale metal-organic frameworks (NMOFs), particularly in the biomedical field, and considering my several years of experience in researching these systems, I found a particular interest in their potential application for treating brain diseases. Hence, I have composed this letter to highlight this topic. NMOFs possess promising advantages that make them appealing for drug delivery purposes. Although, based on the available literature, the research on drug delivery to the brain for treating brain diseases using NMOFs is relatively constrained, in comparison to other drug delivery systems and the delivery of drugs to different body parts using NMOFs. The majority of studies on NMOFs in the context of brain diseases primarily focuses on the diagnosis of these disorders via imaging and sensor-based studies.

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NMOFs exhibit an attractive range of properties such as controlled structure, adjustable porosity, and easy chemical functionalization, which make them a valuable tool in the field of biomedicine [1]. Innovative nanosystems based on functionalized NMOFs have been developed for diagnosing and treating brain disorders (Fig. 1) [2]. In recent years, the advancement of NMOFs has expanded possibilities for providing precise diagnosis and efficient treatment of neurological disorders. Consequently, diagnostic/monitoring techniques based on MOFs, such as neuroimaging and biosensors (utilizing electrochemistry, fluorometry, colorimetry, electrochemiluminescence, etc.), and therapeutic approaches involving enhanced blood-brain barrier (BBB) permeability, targeting precise lesion locations, reduction of neuroinflammation/oxidative stress, and regeneration of nerve cells, have been prominently emphasized for addressing neurological conditions [3]. However, there are still numerous challenges in employing NMOFs for theranostic applications in brain disorders,

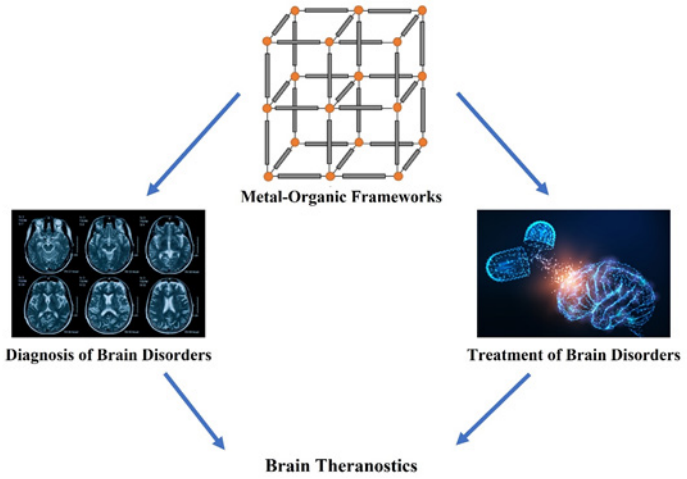

Fig. 1. Metal-organic frameworks in brain theranostics

which limits the use of NMOFs in the diagnosis and treatment of these diseases [3-5]. Firstly, the BBB poses a significant obstacle, impeding the delivery of drug agents from the bloodstream to damaged brain cells. Only select particles necessary for brain function can pass through [6]. The primary role of the BBB is to effectively isolate the neural environment of the brain from the bloodstream, contrasting with the peripheral capillaries which facilitates a more unrestricted exchange of substances between blood and tissues. The BBB, characterized by its tightly sealed capillaries, features the lowest permeability in the entire body owing to physical impediments such as tight junctions. Consisting of a single layer of endothelial cells along the brain capillaries, the BBB serves as a vital barricade that regulates the environment necessary for synapses and neural activity to thrive [7]. Enhancing the efficacy and permeability of NMOFs through suitable functionalization or modification of biological groups can help to overcome this limitation. In crossing the BBB, NMOFs can passively transport based on properties like size, surface properties, and lipophilicity. Thus, chemical modifications can enhance their transport. Alternatively, brain drug delivery can target specific receptors with ligands. Modification of NMOF structures or conjugation with specific ligands helps in recognition by transporters and receptors for effective delivery into the brain [4].

Secondly, the limited stability and high production costs of NMOFs under physiological conditions have restricted their practical use [8]. It is crucial to synthesize NMOFs using simple, cost-effective, efficient, and environmentally friendly techniques (e.g., green synthesis methods) to facilitate their commercialization and scalability.

Thirdly, evaluating the biocompatibility, biodegradability, potential side effects, and biosafety of NMOFs is crucial for their clinical applications [9]. Various factors, such as the nature of the metal and ligand used in the structure of NMOFs, the size of NMOFs, and their surface characteristics can affect their biocompatibility. The surface of NMOFs can be altered to adjust their stability and capacity to remain in the bloodstream until reaching the desired targeted destination. One widely employed method for changing the surface characteristics of NMOFs is through post-synthetic modifications, which involves applying a functional layer onto the surface. Organic polymers, silica shells, and lipid bilayers have been utilized as surface modifiers to enhance the biocompatibility of NMOFs [9]. The biosafety implications of NMOF degradation must be thoroughly examined before their utilization as carriers in biomedical applications. Various factors, including the strength of metal-ligand bonds and environmental conditions, influence the degradation of NMOFs. Of these factors, the pH of bodily fluids emerges as a critical determinant of NMOF degradation and cargo release, underscoring the suitability of MOFs for drug delivery purposes. Furthermore, implementing adjustments like surface modifications can prove advantageous in augmenting the biodegradability of NMOFs [9, 10]. Further, in-vivo research is necessary to more thoroughly evaluate the pharmacokinetic characteristics of these platforms, particularly

regarding their degradability and potential toxicity.

BBB is a critical obstacle in the development of new drugs for the central nervous system. There is a possibility that NMOFs can be utilized for delivering future therapeutics against brain diseases. However, the functional drug delivery mechanism to the brain requires further research and exploration. The existing nanoparticle-based NMOFs must be enhanced to ensure safety, effectiveness, targeted delivery, and cost efficiency. Increased participation and research funding from both the government and corporate sectors are essential to make this vital technology viable. Nevertheless, significant optimization, standardization, and randomization efforts are necessary before its actual clinical application can be realized.

CONCLUSION

In conclusion, despite the potential of NMOFs for treating brain diseases through drug delivery, research in this field is limited. Challenges like the BBB, stability issues, and high costs need to be addressed through functionalization, green synthesis methods, and toxicity analyses. Further optimization is crucial for the safe and effective clinical application of NMOFs in brain disease treatment. Collaboration and funding are essential for advancing this technology and overcoming current barriers to drug delivery to the brain.

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