Development and Mechanistic Modelling of Prussian Blue-based Multimodal Targeted Theranostic Nanocomposite for Cancer Treatment

Thesis submitted by

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Synopsis

Cancer represents one of the most significant health challenges of our time, affecting millions of individuals worldwide and posing a substantial burden on healthcare systems. It is characterized by uncontrolled cell growth, invasion into surrounding tissues, and potential metastasis to distant organs. Its ability to disseminate to distant sites from its point of origin enhances its lethality, amplifying the severity of the disease. Early detection and rapid treatment pay pivotal roles in enhancing cancer survival rates. Any delays in diagnosing and commencing treatment generally lead to an elevated risk of death, as evidenced by numerous studies. Conventional chemotherapy, while a cornerstone in cancer treatment, is hampered by systemic toxicity, drug resistance and non-specific targeting. In addition, conventional cancer diagnostic techniques such as X-rays, CT scans, MRI, and ultrasound to tissue biopsies and blood-based biomarker analysis often suffer limitations such as low sensitivity, invasiveness, inherent long term toxicity, and inability to provide real-time monitoring of treatment response. Specifically, in MRI, patients with impaired kidney function may be at risk of developing Nephrogenic Systemic Fibrosis after exposure to certain gadolinium-based contrast agents, a condition characterized by skin and tissue thickening. Moreover, recent studies have also raised concerns about gadolinium retention in the body, particularly in the brain and bones, prompting questions about long-term health effects. Additionally, there remains a lack of single agent capable of serving dual therapeutic and diagnostic functions in clinical practice. Currently, the comprehensive utilization of nanomaterials in cancer treatment remains underexplored due to challenges such as nanotoxicity due to off-targeted delivery and the bioaccumulation of nanoparticles, which limit their wider application. Given these challenges, there is an urgent requirement for an alternative versatile nanoplatform to address these issues. Notably, one potential solution lies in utilizing of prussian blue based nanoparticles.

Certainly, despite the promising potential of Prussian blue-based nanoparticles in cancer theranostics (PDT, PTT, drug delivery, MRI etc.), several research gaps still exist that warrant further investigation. (a) Understanding the *in-vitro* and *in-vivo* stability and biodegrability of prussian blue based NPs is crucial for their long-term safety and efficecy. Research is needed to assess their behaviour in biological environments, including their degradation kinetics and potential accumulation in organ over time. (b) Investigating the immunogenicity and biodistribution of prussian blue based NPs for assessing their systemic effects and potential immune responses. Further research is needed to understand how these nanoparticles interact with the immune system and how their biodistribution impacts overall therapeutic efficacy. (b) While prussian blue-based NPs can be functionalized for targeted delivery to cancer cells, the mechanisms underlying targeting specificity need to be elucidated further. Research is needed to explore the interactions between NP surface ligands and cancer cell receptors to enhance targeting efficiency and reduce off-target effects and to develop a novel functionalization approach. (c) Research is needed to optimize the loading and release kinetics of therapeuti payloads within prussian blue-based NPs. This includes investigating various drug encapsulation strategies, as well as assessing the release profiles and bioavailability of loaded drugs in cancer cells. (d) Integrating multimodal theranostic modalities into functionalized prussian blue-based nanocomposite for cancer treatment, requires further research. This includes developing novel imaging agents or conjugation strategies to enable simultaneous imaging and therapy monitoring *in-vivo*. In this context, it is also crucial to take some strategy to modify core prussian blue NPs itself for improving their inherent theranostic efficiency. (e) Bridging the gap between preclinical studies and clinical translation is essential for the practical application of prussian blue-based nanoparticles in cancer theranostics. Research is needed to address regulatory hurdles, optimize manufacturing processes, and conduct rigorous clinical trials to evaluate safety and efficacy in human patients. (f) Furthermore, there exists a scarcity of comprehensive studies regarding the impact of particle size, shape, various functionalizations, doping variations, etc., on the modulation of r_1 and r_2 relaxivity. There is a pressing need for research aimed at delving into this fundamental understanding and developing a dual-modal MRI contrast agent capable of both T_1 and T_2-weighted imaging.

Addressing these research gaps will contribute to the continued advancement of prussian blue-based nanocomposite as versatile agent for cancer diagnosis, imaging, and therapy. Based on these the specefic objectives are outlined as follows:

- Optimization of synthesis protocol to achieve optimal size and shape of PBNPs.
- Devlopment of novel functionalization approach to enhance biocompatibility, enable receptor based targeting and mitigate off target effects.
- Devlopment of prussian blue based NPs with enhanced theranostic capability including PTT, PDT, and improved performance in both T_1-T_2W MR imaging.
- Utilization of hydrophobic natural flabonoid in targeted cancer theranostic applications involving prussian blue based NPs as drug carrier.
- Understanding of the relation between T_1-T_2W MRI relaxivities and influencing parameters like NPs size variation, several modifications and various doping.

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