

**Université Paris Cité**

**Research Proposal**

*Optimizing Nanoparticle Coatings for Enhanced Hydrogel-Tissue Adhesion in Surgical and Regenerative Applications: Exploring Blood Coagulation Mechanisms, In Vivo Performance, and Long-Term Biointegration*

**Presented to  
Université Paris Cité**

**Joseph Clark SHETTIMA**

**8 January, 2025**

## Table of Content

Table of Content .....	2
Abstract.....	3
Chapter 1.....	4
1. Introduction .....	4
1.1 Background of the Study .....	4
1.2 Problem Statement.....	4
1.3 Research Objectives .....	4
1.4 Significance of the Study.....	5
Chapter 2.....	6
2. Literature Review .....	6
2.1 Surgical Adhesives and Tissue Response.....	6
2.2 Nanoparticle Interactions with Blood Coagulation .....	6
2.3 Autofluorescent Nanoparticles for Biomedical Applications.....	6
2.4 Hydrogel Adhesion and Nanoparticle Functionalization .....	6
3. Research Methodology .....	7
3.1 Material Preparation and Nanoparticle Coating .....	7
3.2 In Vitro Testing .....	7
3.3 In Vivo Testing.....	7
3.4 Biocompatibility and Safety Assessment .....	7
3.5 Statistical Analysis .....	7
Chapter 4.....	8
4. Expected Outcomes and Impact .....	8
References .....	9

## **Abstract**

The adhesion of hydrogels to biological tissues is a longstanding challenge in tissue engineering, implantable devices, and surgical adhesives. Hydrogel-based materials are favored for their biocompatibility, flexibility, and similarity to soft tissues; however, their poor adhesion limits their application in regenerative medicine and surgical procedures. Recent advancements, such as the use of silica nanoparticles, have shown promise in enhancing hydrogel-tissue adhesion through blood coagulation mechanisms, forming a natural adhesive joint at the tissue interface (Michel et al., 2020). This research aims to optimize silica nanoparticle coatings to enhance adhesion strength under dynamic in vivo conditions, investigate the underlying mechanisms of blood coagulation, and evaluate long-term biointegration. The results are expected to provide breakthroughs in hydrogel-based materials for tissue repair, surgical adhesives, and hemostatic agents.

# Chapter 1

## 1. Introduction

### 1.1 Background of the Study

Hydrogels are widely utilized in various biomedical applications, including tissue engineering, drug delivery, and wound healing, due to their high water content and biocompatibility. Despite these advantages, their poor adhesion to biological tissues severely limits their efficacy in surgical and implantable applications (Toriumi, 2020). To address these challenges, chemical surface modifications and adhesion promoters have been explored, but these methods often result in cytotoxicity, complex preparation processes, and inconsistent outcomes. Recent innovations suggest that silica nanoparticles, owing to their high surface area, stability, and biocompatibility, can adsorb onto hydrogel surfaces to promote blood coagulation and form adhesive joints with tissues (Michel et al., 2020).

### 1.2 Problem Statement

Despite promising results in *ex vivo* studies, the *in vivo* performance of silica nanoparticle-coated hydrogels remains limited by variability in tissue-specific responses, dynamic biological environments, and long-term material stability. Critical questions remain about optimizing nanoparticle properties, such as size and surface area, to improve hydrogel adhesion strength and understanding the mechanisms by which nanoparticles influence blood coagulation *in vivo* (Zhang et al., 2022).

### 1.3 Research Objectives

1. Investigate the role of silica nanoparticles in enhancing hydrogel-tissue adhesion via blood coagulation mechanisms.
2. Optimize the surface characteristics (size, surface area, functionalization) of silica nanoparticles to improve adhesion strength *in vivo*.
3. Evaluate the long-term biointegration and stability of nanoparticle-coated hydrogels in various tissue environments.
4. Assess the biocompatibility, safety, and biodegradability of silica nanoparticle coatings for clinical applications.

#### **1.4 Significance of the Study**

This study has the potential to significantly advance the field of hydrogel-based biomaterials by addressing their adhesion limitations. Optimized nanoparticle coatings can lead to breakthroughs in surgical adhesives, tissue repair materials, and hemostatic agents, with broad applications in regenerative medicine, minimally invasive surgeries, and implantable devices. By improving adhesion strength and understanding biointegration mechanisms, this research aims to enhance patient outcomes and reduce surgical complications.

## Chapter 2

### 2. Literature Review

#### 2.1 Surgical Adhesives and Tissue Response

(Toriumi, 2020) explored the host tissue response and adhesive strength of surgical adhesives, emphasizing that successful adhesion depends on biocompatibility and the capacity to integrate with the surrounding tissue. This study highlights the importance of optimizing adhesive formulations for clinical performance.

#### 2.2 Nanoparticle Interactions with Blood Coagulation

(Gryshchuk & Galagan, 2016) studied silica nanoparticles' effects on blood coagulation proteins and platelets, demonstrating their ability to enhance clot formation by interacting with coagulation pathways. This finding underpins the potential of silica nanoparticles in hydrogel-based tissue adhesives.

(Tran et al., 2022) provided a comprehensive analysis of nanoparticles' interface with the blood coagulation system, focusing on their ability to trigger and stabilize clots. These mechanisms are critical for developing adhesives that function effectively *in vivo*.

#### 2.3 Autofluorescent Nanoparticles for Biomedical Applications

(Wey & Epple, 2020) discussed the use of ultrasmall nanoparticles as autofluorescent labels, emphasizing their biocompatibility and potential for biomedical applications. Although primarily focused on imaging, these insights are relevant for designing nanoparticles that interact effectively with biological systems.

#### 2.4 Hydrogel Adhesion and Nanoparticle Functionalization

(Michel et al., 2020) demonstrated that silica nanoparticles enhance hydrogel-tissue adhesion by inducing blood coagulation. Their study showed a 2- to 4-fold increase in adhesion energy and rapid hemostatic capabilities, making this approach suitable for surgical applications.

These studies collectively underscore the promise of nanoparticle-functionalized hydrogels for improving tissue adhesion and integration. Building on these insights, the proposed research seeks to optimize nanoparticle coatings for enhanced *in vivo* performance.

## Chapter 3

### 3. Research Methodology

#### 3.1 Material Preparation and Nanoparticle Coating

Poly(ethylene glycol) (PEG)-based hydrogels will serve as the model substrate due to their well-documented biomedical applications (Toriumi, 2020). Silica nanoparticles with varying surface functionalities (e.g., amine, carboxyl) will be synthesized and adsorbed onto hydrogel surfaces.

#### 3.2 In Vitro Testing

- **Adhesion Strength Tests:** Peel and pull-off tests using pig liver tissue as a model.
- **Blood Coagulation Assays:** Confocal microscopy and clotting time analysis to observe clot formation at the hydrogel-tissue interface (Tran et al., 2022).

#### 3.3 In Vivo Testing

- **Animal Models:** Adhesion strength and tissue responses will be assessed in pig and rat models at multiple time points (e.g., 1 hour, 24 hours, 7 days, 30 days).
- **Histological Analysis:** Tissue response and healing will be evaluated through cytokine measurements and microscopy (Zhang & Wang, 2022).

#### 3.4 Biocompatibility and Safety Assessment

- **Methods:** Histopathological analysis, blood chemistry studies, and immunohistochemical staining will be conducted to assess biocompatibility and biodegradability (Toriumi, 2020).

#### 3.5 Statistical Analysis

Data will be analyzed using statistical methods, including ANOVA and t-tests, with a significance level of  $p < 0.05$ . Results will be compared to controls to evaluate improvements in adhesion and biocompatibility.

## Chapter 4

### 4. Expected Outcomes and Impact

1. Identification of optimal silica nanoparticle properties for enhanced hydrogel adhesion.
2. Mechanistic insights into blood coagulation at the hydrogel-tissue interface.
3. Improved in vivo performance and biointegration of nanoparticle-coated hydrogels.
4. Development of safe, effective hydrogel-based adhesives for clinical applications.

## References

1. Gryshchuk, V., & Galagan, N. (2016). Silica nanoparticles effects on blood coagulation proteins and platelets. *Biochemistry Research International*, 2016, 1–6. <https://doi.org/10.1155/2016/2959414>
2. Michel, R., Roquart, M., Llusar, E., Gaslain, F., Norvez, S., Baik, J. S., Yi, G.-R., Manassero, M., & Corté, L. (2020). Hydrogel-tissue adhesion using blood coagulation induced by silica nanoparticle coatings. *ACS Applied Bio Materials*, 3(12), 8808–8819. <https://doi.org/10.1021/acsabm.0c01158>
3. Toriumi, D. (2020). Surgical tissue adhesives: Host tissue response, adhesive strength and clinical performance. *Surgical Adhesives and Sealants*, 61–69. <https://doi.org/10.1201/9780429332500-9>
4. Tran, H. D. N., Akther, F., Xu, Z. P., & Ta, H. T. (2022). Effects of nanoparticles on the blood coagulation system. *Nanotechnology for Hematology, Blood Transfusion, and Artificial Blood*, 113–140. <https://doi.org/10.1016/b978-0-12-823971-1.00007-6>
5. Wey, K., & Epple, M. (2020). Ultrasmall gold and silver/gold nanoparticles (2 nm) as autofluorescent labels for poly(D,L-lactide-co-glycolide) nanoparticles (140 nm). *Journal of Materials Science: Materials in Medicine*, 31(12). <https://doi.org/10.1007/s10856-020-06449-8>
6. Zhang, J., & Wang, Z. (2022). Nanoparticle–Hydrogel Based Sensors: Synthesis and Applications. *Catalysts*, 12(10), 1096. <https://doi.org/10.3390/catal12101096>