



RESEARCH PROPOSAL 2025

Proposal by

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PhD Research Proposal

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Proposed Field: Inorganic Chemistry
(Specialization in Bioinorganic Chemistry)

Proposed Title:
Design and Development of Artificial
Metalloenzymes as Targeted Therapeutic
Agents for Cancer Treatment

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INTRODUCTION

Cancer remains one of the leading causes of mortality globally, necessitating the development of targeted therapies that minimize side effects and improve treatment efficacy. Bioinorganic chemistry, particularly the use of metal-based agents, has shown significant promise in therapeutic applications. Natural metalloenzymes play critical roles in biological processes, but their therapeutic use is limited by issues like instability and non-specificity.

Artificial metalloenzymes (ArMs)—engineered combinations of synthetic metal complexes and protein scaffolds—offer a powerful solution. They can be tailored to perform specific catalytic reactions within targeted environments, including tumor tissues. This project aims to design novel ArMs capable of delivering selective cytotoxic effects against cancer cells.

RESEARCH PROBLEM

Despite the availability of metal-based drugs like cisplatin, major limitations include non-specific toxicity and drug resistance. There is a need to develop next-generation, metal-based therapeutic systems that can operate selectively within cancerous cells. Artificial metalloenzymes represent an innovative approach, but their biomedical application—especially in oncology—remains underdeveloped.

RESEARCH OBJECTIVES

1. To design and synthesize artificial metalloenzymes based on biocompatible protein scaffolds and transition metal complexes.
2. To evaluate their ability to catalyze bioorthogonal reactions selectively within cancer cells.
3. To assess the cytotoxic efficacy and specificity of these ArMs in vitro and in vivo.
4. To optimize stability, biocompatibility, and catalytic turnover under physiological conditions.

LITERATURE REVIEW SUMMARY

The recent SABIC 2024 symposium emphasized the growing role of metals in medicine, particularly in the context of metalloenzymes and metal-based therapeutic agents. Studies show that metals like Ru, Ir, and Cu can catalyze reactions useful in anticancer strategies, including reactive oxygen species (ROS) generation and prodrug activation. ArMs, combining these metal centers with protein scaffolds, have demonstrated preliminary success in catalyzing unique, tumor-specific reactions—yet much remains unexplored, particularly in clinical relevance and target

METHODOLOGY

5.1. Design & Synthesis:

- Select biocompatible scaffolds (e.g., streptavidin, albumin).
- Introduce transition metal complexes (Ru, Ir, Cu) as catalytic centers.
- Use site-directed mutagenesis for specific binding pocket engineering.

5.2. Characterization:

- Techniques: UV-Vis spectroscopy, Circular Dichroism (CD), EPR, NMR, Mass Spectrometry, X-ray crystallography.
- Validate metal incorporation and protein structure.

5.3. In Vitro Evaluation:

- Test in cancer cell lines (e.g., HeLa, MCF-7).
- Analyze cell viability (MTT/XTT assays), apoptosis (Annexin V staining), and ROS generation.

5.4. In Vivo Evaluation:

- Use mouse xenograft models.
- Study biodistribution, tumor suppression, and systemic toxicity.

EXPECTED OUTCOMES

- Development of stable, selective ArMs with high catalytic turnover.
- Demonstrated ability to activate prodrugs or generate ROS in cancer cells.
- Proof-of-concept for a new class of targeted cancer therapeutics.

RESEARCH TIMELINE

Year 1 : Literature review, design of scaffolds and metal complexes

Year 2 : Synthesis and characterization of ArMs

Year 3 : In vitro testing and optimization

Year 4 : In vivo testing, data analysis, and thesis writing

SIGNIFICANCE OF THE STUDY

This research addresses an urgent clinical need: more selective and effective cancer therapies. The integration of inorganic chemistry and biotechnology through ArMs could revolutionize targeted drug design. Successful completion may lead to a new class of therapeutics that are both potent and precise, paving the way for metal-based personalized medicine.

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