Final Project

NANO103: Foundations in Nanoengineering: Biochemical Principles

Deadline: Friday 14 Jun @11:59PM (Midnight)

University of California, San Diego
Prof. Zeinab Jahed

Academic Integrity
You are expected to work in groups of two on this project. Any consultation or collaboration with other groups is not permitted and considered a violation of the course's academic integrity guidelines. This document is not to be shared with anyone. Any distribution, including emailing, posting on message boards, texting or submitting to "homework help" style websites of this document, its contents will be considered a violation of the course's academic integrity guidelines.

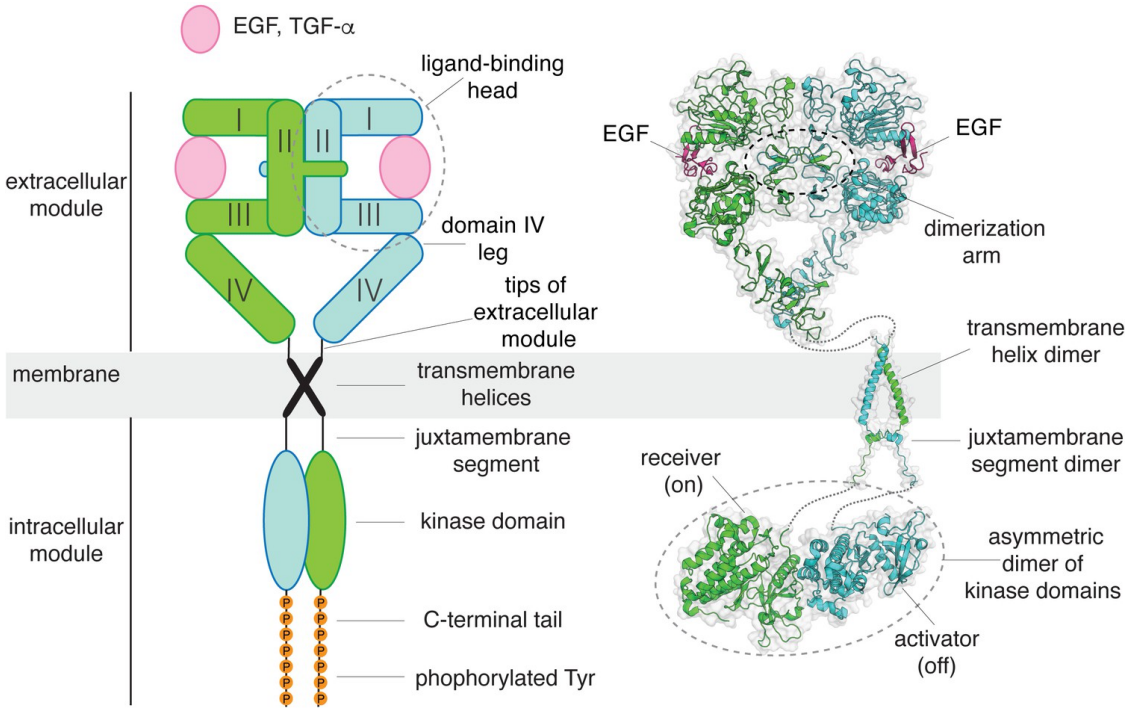
Submission Details:
Create a PDF report with the following guidelines:

- Write a brief, one sentence statement acknowledging that you have read and understood the Academic Integrity guidelines summarized at the top of the first page of this file and that you have completed the assignment with integrity.
- This exam is open book and open note. Include references to any online resources used. You can use a referencing style of your choice.
- Submit all images, plots and text embedded in a single PDF. Present your results as a report.
- **Your figures and plot should be properly labeled and legible.**

Project Title: Designing a Protein Inhibitor and Nanocarrier for the EGFR Receptor in Cancer Cells

Project Overview

You are tasked with designing, manufacturing, and delivering a protein inhibitor targeting the ligand binding region of the Epidermal Growth Factor Receptor (EGFR), a key receptor involved in the proliferation of certain cancer cells. The structure of this receptor is shown below (from Huang et al. 2021, elife)



Part I. Background Research (30 points)

Objective: Understand the role of EGFR in cancer based on structural data.

- **Tasks**:
  A. Research the structure and function of EGFR extracellular and intra-cellular domains. Provide a ~1 page summary of the structure and function. Include VMD images of the structure(s) of EGFR where applicable.
  B. Explore the structural features of the transmembrane domain of EGFR. Include and analyze the hydropathy plot (a screen shot from the pdb website is acceptable).
  C. Based on the structure and function of EGFR, explore the significance of targeting EGFR in cancer therapy.

Hint: The. pbd accession codes for structures of various domains of EGFR are provided in the manuscript by Huang et al. 2021, elife.

Part II. Protein Inhibitor Design and Manufacturing (40 points)

Objective: Design and manufacture a novel protein inhibitor for EGFR.

- **Tasks**:
  A. Analyze the EGFR lignad (EGF) binding site (PDB ID: 3NJP).
  B. Design a protein/peptide that is 15-25 residues long and can bind to the EGFR active site and inhibit its function. Explain your work.
  C. Predict the structure of your inhibitor protein/peptide using alphafold and include it in your report.
  D. After designing your inhibitor protein/peptide, you will express it in bacteria using circular plasmids for manufacturing.

     i. Identify the DNA sequence of the designed inhibitor protein/peptide and design and evaluate primers to amplify it. Describe the PCR protocol to amplify the inhibitor gene.
     ii. Design a DNA plasmid to express your inhibitor protein/peptide in Ecoli. Use benchling to display the circular plasmid and all its components. Explain your work in detail. Outline the steps for cloning the amplified gene into an expression vector.

Hint 1: You can draw inspiration from the structure of the ligand bound to EGFR for designing a inhibitor protein/peptide. **Hint 2:** Many online servers can reverse translate a protein sequence into a DNA sequence.

Part III. Design of Lipid Nanoparticles (LNP) for Targeted Peptide Delivery (30 points)

Objective: Design a lipid-based nanocarrier (liposome) for delivering the protein inhibitor to cancer cells.

- **Tasks**:

  A. Design an LNP formulation that can encapsulate the protein inhibitor.
  B. Incorporate targeting ligands on the LNP surface to enhance specificity for cancer cells expressing EGFR.
  C. Determine and discuss the optimal loading method for the protein inhibitor based on its hydrophobicity or hydrophilicity.