Project Title:

Development of AI-based PROTAC drug design platform and its demo application

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Project Abstract/Proposal Summary:

PROTAC (Proteolysis Targeting Chimera) technology is a groundbreaking approach that leverages the ubiquitin-proteasome pathway to degrade disease-related proteins. It holds transformative potential by addressing the challenge of "undruggable" targets—proteins that lack binding pockets suitable for traditional small molecule drugs. Despite its promise, designing effective PROTAC molecules is hindered by the vast chemical space and complex requirements such as binding affinity, solubility, and pharmacokinetics. This project aims to bridge this gap by developing an AI- and molecular simulation-based platform for PROTAC drug design.

The platform integrates machine learning (ML) and molecular dynamics (MD) simulations, creating a pipeline for generating, refining, and evaluating PROTAC molecules. In the ML phase, a transformer-based neural network, Proformer, will generate candidate molecules using data pre-trained on the ZINC database and fine-tuned with PROTAC-specific datasets. Reinforcement learning will enhance these molecules to optimize pharmacokinetic properties. The MD phase will employ advanced techniques, including molecular docking, free energy perturbation, and binding affinity analysis, to screen for the most promising candidates.

To demonstrate the platform's efficacy, the project will focus on designing PROTACs targeting BTK and BRD4 proteins, which are implicated in cancer and inflammation. These molecules will undergo experimental validation in collaboration with industry and academic partners. The project's outcome will fill a critical technical and commercial void, offering pharmaceutical companies and research institutions an efficient and cost-effective solution for PROTAC drug development.

With its multidisciplinary approach and the principal investigator's expertise, this initiative has the potential to revolutionize the field of targeted protein degradation and accelerate therapeutic advancements.