Offer: PhD on AI models in protein design (CEA Grenoble)
(with opportunity for a Master 2 internship in 2026)

Integration of Quantum Mechanical Modeling and Artificial Intelligence for Design of Therapeutic Proteins

The development of effective therapeutic proteins remains a complex computational challenge requiring detailed understanding of molecular interactions at the atomistic level. While recent advances in deep learning-based generative models (RFdiffusion, ProteinMPNN) have revolutionized the ability to generate protein structures de novo, these approaches often lack the physical precision necessary to accurately characterize the energetic interactions critical for binding affinity and functional specificity.

Background

Designing functional and therapeutically relevant proteins requires balancing the creative exploration capabilities of generative AI with the rigorous physical foundations of quantum chemistry. Recent advances such as RFdiffusion and ProteinMPNN have transformed ***de novo* protein design** by learning structural and sequence patterns directly from large-scale biological data. However, these models operate primarily on statistical representations of molecular structure, without explicit incorporation of first-principles physical observables. As a result, their exploration of backbone and side-chain conformational space remains limited by the lack of explicit information on geometric feasibility, energetic optimality, and chemical consistency with the target interaction.Integrating ab initio, non-parametric descriptors from **density functional theory (DFT)** into generative frameworks introduces physically grounded constraints, such as local electronic environments, bond polarization, and energy decomposition terms, that can steer the generative process toward quantum-consistent conformations and interactions, enhancing both design accuracy and functional relevance.

Objective

To develop an innovative computational pipeline that integrates ab initio quantum mechanical calculations (DFT) with generative artificial intelligence models for the design of therapeutic proteins with high affinity and specificity. The approach will combine:

1. Quantum mechanical characterization using a high-performance parallel DFT implementation to extract key observables including fragment-resolved interaction energies, bond orders, dispersion interactions, short-range chemical interactions, long-range electrostatic contributions, ..
2. Physics-guided structural generation via RFdiffusion with physical constraints derived from DFT observables
3. Sequential optimization through ProteinMPNN to maximize stability and expressibility

Workplan
The PhD student will develop and validate an integrated computational pipeline combining quantum mechanical precision with generative AI capabilities for therapeutic protein design. After mastering the BigDFT software and QM/CR approach for quantum-level analysis of protein interactions, along with state-of-the-art generative models (RFdiffusion, ProteinMPNN), the student will develop workflows to incorporate DFT-derived physical constraints into AI-guided structure generation. The methodology will be validated on benchmark systems before application to the clinically relevant PD-L1/KN035 nanobody complex for **cancer immunotherapy**, performing systematic mutation studies to identify variants with improved binding affinity and stability. Finally, the approach will be extended to additional therapeutic targets including antimicrobial and antiviral applications, with results published in high-impact journals and presented at international conferences.

Host laboratory
The PhD will be hosted at the **Interdisciplinary Research Institute of Grenoble (IRIG)**, CEA Grenoble. The student will be co-supervised by Dr. Luigi Genovese (L_Sim group, MEM laboratory) expert in *ab initio* quantum mechanical simulations and lead developer of the BigDFT software package, and Dr. Guido Uguzzoni (Biosciences et Bioingénierie pour la Santé - BGE laboratory) expert in machine learning and artificial intelligence for protein design.
The PhD student will evolve in the rich scientific ecosystem of CEA Grenoble, with access to high-performance computing facilities and opportunities for interactions with computational scientists, structural biologists, and AI researchers from multiple laboratories.

Candidate profile
Master's degree in computational or statistical physics, computational chemistry, bioinformatics or related field. Strong background in machine learning. Proficiency in scientific programming (Python and/or Julia/C++) and Linux/Unix environments. The candidate should demonstrate curiosity, analytical skills, and the ability to work in multidisciplinary teams. Good communication skills in English for scientific publications and presentations.

Job contract
3-year PhD contract starting in October 2026 (or upon agreement) with opportunity for a Master 2 internship starting February 2026.
Competitive PhD salary according to French regulations, with full social security benefits.
Application: Please send a CV, a cover letter explaining your motivation and relevant experience, academic transcripts, and the names of two referees to:
luigi.genovese@cea.fr and **guido.uguzzoni@cea.fr**