Digital Diagnostics: In Silico Design of Aptamers for Early Alzheimer's Detection via PDGFR-β Binding

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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, memory impairment, and neuronal dysfunction. Early diagnosis is critical for improving patient out- comes, yet current detection methods remain limited in sensitivity and accessibility. Platelet-derived growth factor receptor beta (PDGFR-β), a biomarker linked to blood–brain barrier integrity and neurovascular dysfunction, has emerged as a promising target for early AD detection. In this study, we employed an in-silico approach to design and evaluate aptamers with high binding affinity for PDGFR-β. Protein structures were modeled using UniProt and AlphaFold, and potential binding sites were predicted with ScanNet, identifying the D2 extracellular domain as the most favorable target. Molecular docking simulations were performed with HDOCK, followed by detailed interaction profiling using PLIP and RinMaker. Binding free energies were calculated with PRODIGY to assess thermodynamic stability. The results demonstrated stable interactions, including hydrogen bonding, hydrophobic contacts, and salt bridges, with favorable ΔG values supporting strong aptamer–protein binding. These findings highlight the feasibility of computationally designed aptamers as diagnostic probes for PDGFR-β, providing a cost-effective and rapid approach for early-phase research. While experimental validation is required to confirm specificity and stability in biological systems, this work establishes a foundation for aptamer-based biosensors and diagnostic assays aimed at enabling earlier detection of AD.

1. INTRODUCTION

Alzheimer's disease (AD) is a progressive neurological disorder that affects the brain, leading to memory loss, cognitive impairment, and behavioral changes. [10] It is the most common cause of dementia in older adults and results from the buildup of ab- normal proteins, such as amyloid plaques and tau tangles, which damage brain cells and disrupt communication between neurons. [13] Early symptoms include forgetfulness, confusion, trouble with language, and difficulty completing familiar tasks. [3] As the disease progresses, individuals may experience disorientation, mood swings, and eventually lose the ability to recognize loved ones or care for themselves. [3] These symptoms gradually worsen, making AD a deeply challenging condition for both patients and caregivers. Diagnosis currently involves cognitive tests, neurological exams, and brain imaging techniques such as MRI and PET scans. A newer, less invasive option is the FDA-approved Lumipulse blood test, which detects amyloid protein levels in the blood. Treatments such as donepezil and memantine can help manage symptoms, while newer drugs like Lecanemab and Donanemab aim to slow disease progression by targeting amyloid buildup. Research is ongoing to develop earlier detection methods and more effective therapies. [2] Molecular docking is a computational strategy that predicts the interaction of two molecules, a protein and a small molecule (ligand), often in advance. [4] It forecasts the most ideal orientation and binding ability of the ligand to the active site of the protein, providing insight into molecular recognition and stability. [6] This method is commonly applied in drug discovery, structural biology, and bioinformatics. [1] It allows one to screen potential compounds inexpensively, which aids in the identification of the most likely compounds that can bind effectively to a target protein. Several software packages carry out molecular docking, including AutoDock, Glide, MOE, GOLD, and Swiss- Dock. In our work, we used the HDOCK platform, a robust platform for protein-ligand and protein-protein docking. [15] Molecular docking is used to identify drug leads, investigate enzyme interactions, predict the effect of mutations, and explore protein-protein interactions. Molecular docking enables the initial phases of investigation by reducing the need for extensive laboratory experimentation. Antibodies are proteins made by the immune system that help the body fight off infections and other harmful substances. [9] They recognize and attach to specific antigens, such as bacteria, viruses, or other particles, and mark them for destruction by other immune cells. Antibodies are essential for protecting the body from disease and play a central role in how the immune system identifies and eliminates threats. In research, antibodies are also used as biomarkers, as their presence or interaction with specific proteins can indicate

signs of disease.

The platelet-derived growth factor receptor (PDGFR), is a receptor protein that binds to platelet-derived growth factors to regulate cell growth, survival, and repair. [5] Its beta form, PDGFR-β, is especially important in the study of AD. [5] Vrillon et al. have shown that PDGFR-β is present in the cerebrospinal fluid (CSF) of individuals with AD, where it signals blood-brain barrier (BBB) breakdown and vascular dysfunction, both of which are closely tied to the progression of the disease. [12] PDGFR-β is also vital for maintaining the function of pericytes. These cells support and stabilize blood vessels in the brain, meaning its disruption can have serious consequences for brain health. While AD is a primary focus of PDGFR-β research, abnormal activity of this protein has also been observed in cancer. [5] In cancer, PDGFR-β contributes to uncontrolled cell growth and survival, making it a key factor in tumor development and spread. Its dual involvement in both cancer and AD highlights the broad significance of PDGFR-β in human disease. However, in the context of neurodegeneration, its detection in CSF provides an especially valuable biomarker for AD diagnosis and progression, which makes it a major target for ongoing studies in neurological health.

2. METHOD

PDGFR-β modeling involves utilizing several computational tools and databases to gather accurate information about the protein's structure, function, and interactions. UniProt (Universal Protein Resource) is a comprehensive, high-quality database of protein sequences and functional information that researchers use to obtain curated protein structure, function, and interaction data in order to support biological and biomedical research. [11] We used it to obtain valid and updated information about proteins relevant to our study, enabling proper analysis and interpretation. AlphaFold, an advanced artificial intelligence technology developed by DeepMind, precisely predicts a protein's 3D structure from its amino acid sequence, allowing scientists to understand better how proteins function and interact. [1] We used it to visualize and document the 3D structures of our protein of interest. Additionally, ScanNet was used to obtain accurate models of PDGFR and PDGFR-β, and the predicted binding site was identified as D2 on the PDGFR-β molecule. [8] For molecular docking simulations, We used HDOCK, a computer program that forecasts the interaction of two molecules by simulating how they interlock and the strength and type of binding. [15] This allowed us to simulate and screen how possible ligands bind to our target protein to identify suitable candidates for further investigation. We also used several tools to study protein binding energy and ligand interactions. PLIP and RinMaker provided bond count and structural analysis, while PRODIGY (PROtein binDIng enerGY prediction) was used to calculate the binding free energy (ΔG) in kcal mol^{-1} between two protein partners in our study. [7, 14] By uploading PDB files of the protein complexes, PRODIGY analyzed the interfacial interactions and generated ΔG values, giving insight into thermodynamic stability and binding strength. PLIP (Protein–Ligand Interaction Profiler) was then used to identify and analyze non-covalent interactions, such as hydrogen bonds, hydrophobic interactions, salt bridges, and π-stacking, within each protein-ligand complex. {Salentin, 2015 #769} By uploading the PDB files to PLIP, we obtained a detailed breakdown of stabilizing interactions, allowing us to compare binding profiles across different ligands and protein conformations. This comprehensive analysis enabled us to interpret the functional relevance of binding sites, assess the strength and specificity of binding events, and inform further computational or experimental studies.

In the next step, we computed the binding energy of the PDGFR–antibody complex, calculated using the PRODIGY software, Figure 4. The values, expressed in kcal/mol, quantify the thermodynamic strength of the interaction between the receptor and antibody. Lower binding energy values indicate a stronger and more stable complex, allowing for conclusions to be drawn about the most effective binding antibody.

3. DISCUSSION

Application: The applications of this research are centered on the early detection of AD through the targeting of PDGFR-β, a biomarker associated with BBB integrity and neurodegeneration.{Abbott, 2010 #896} By identifying and optimizing antibodies, short, single-stranded nucleic acids that bind specifically to target molecules, this study leverages computational tools to predict the strongest binding candidates for PDGFR-β.{Abbott, 2010 #788} These aptamers could then be utilized in diagnostic assays or biosensors to detect subtle changes in PDGFR-β levels at the onset of AD, potentially enabling earlier diagnosis than current methods allow.{Camorani, 2014 #1404}{Vrillon, 2025 #1544} Early detection is critical in slowing disease progression, improving patient outcomes, and guiding timely therapeutic interventions, making this approach a valuable step toward more effective AD diagnostics.

This study demonstrates the potential of computationally designed aptamers targeting PDGFR-β as promising diagnostic candidates for early-stage Alzheimer's disease (AD). PDGFR-β has emerged as an important biomarker associated with blood–brain barrier (BBB) disruption and neurovascular dysfunction, both of which are strongly linked to AD progression. By focusing on the D2 extracellular domain of PDGFR-β, the molecular docking simulations identified stable aptamer–protein complexes with favorable binding characteristics, suggesting that the selected aptamers may effectively recognize and bind the receptor in biological systems. The combination of hydrogen bonds, hydrophobic interactions, salt bridges, and π-stacking interactions observed in the docking analysis further supports the structural stability and specificity of the complexes. The binding energy calculations generated using PRODIGY showed thermodynamically favorable ΔG values, indicating strong affinity between the aptamers and PDGFR-β. Lower binding energy values generally correspond to more stable molecular complexes, which is an important requirement for diagnostic probes intended for biosensor applications. These findings suggest that the designed aptamers may possess sufficient binding strength to detect subtle changes in PDGFR-β concentration associated with BBB dysfunction during the early stages of AD. The use of computational tools such as HDOCK, PLIP, RinMaker, and ScanNet allowed rapid screening and structural analysis without the immediate need for costly laboratory experiments, demonstrating the efficiency of in silico approaches in biomarker discovery. Future research may also explore integrating these aptamers into portable biosensing technologies for real-time AD screening. Combining aptamer-based diagnostics with machine learning and nanotechnology could improve sensitivity and enable multiplex detection of several AD biomarkers simultaneously. Furthermore, optimizing aptamer sequences through mutation analysis and secondary structure refinement may further enhance binding affinity and diagnostic performance.

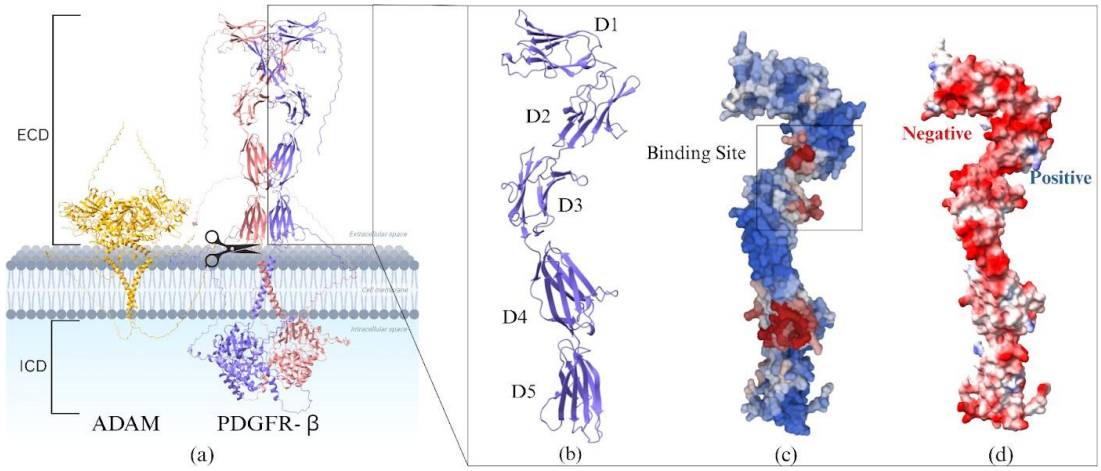

Fig. 1. PDGFR can be modified through cleavage by enzymes from the ADAM family. This process involves cutting the receptor near its outer region, which leads to the release of part of the molecule outside the cell. The remaining portion stays in the membrane and is often referred to as a C-terminal fragment. The portion that gets released outside the cell is known as PDGFR- β; (b) 5 domains of ECD (D1-D5) in subsection b of figure 2, the five domains of the ECD (Extracellular Domain) is shown. D2 is the desired binding site; (c) Predicted binding site: The ScanNet Server was used to predict a possible binding site on the protein by analyzing its structure. After uploading the protein model, the server used machine learning to highlight areas on the surface that are likely involved in binding. It provided a visual output along with scores indicating which regions are most likely to serve as binding sites. D2 was chosen as the most ideal binding ChimeraX software, subsection d of Figure 2 was modeled. This model shows the polarity of the PDGFR-β molecule. This chart presents the molecular interactions within the PDGFR–antibody complex, as identified using PLIP software. The visualization highlights four key types of interactions that stabilize the complex: hydrophobic interactions (blue), hydrogen bonds (green), salt bridges (brown), and π-stacking interactions (red).

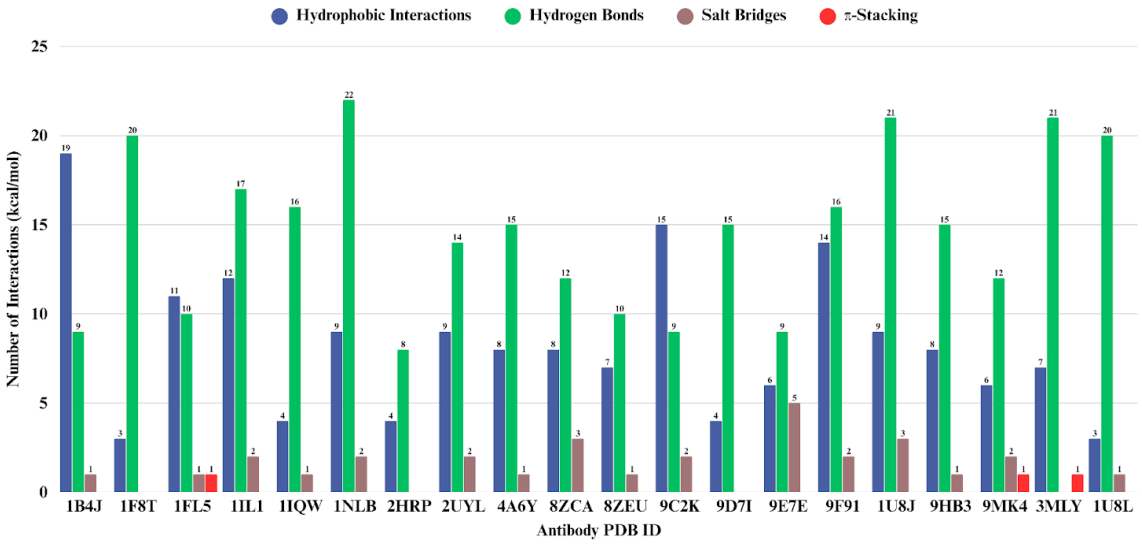

Fig. 2. Molecular interaction profile of the PDGFR–aptamer complexes generated using PLIP analysis. The bar graph compares the number of hydrophobic interactions (blue), hydrogen bonds (green), salt bridges (brown), and π-stacking interactions (red) formed between PDGFR-β and different aptamer PDB models. Hydrogen bonding was the most dominant interaction across the complexes, indicating strong binding stability and specificity, while hydrophobic interactions and salt bridges further contributed to stabilization of the aptamer–protein complexes. π-stacking interactions were observed in selected complexes, suggesting additional non-covalent stabilization within the binding interface.

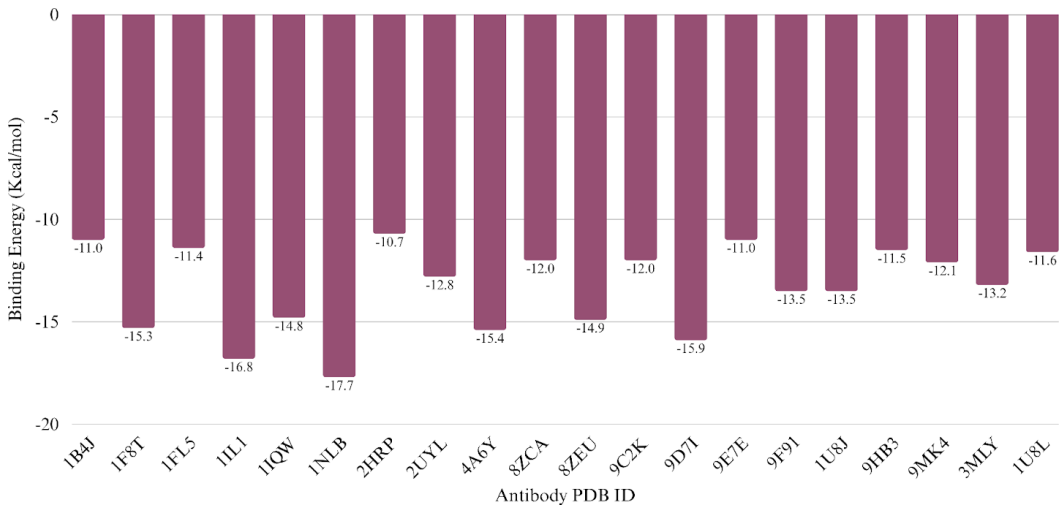

Fig. 3. Predicted binding free energy (ΔG, kcal/mol) of the PDGFR–aptamer complexes calculated using the PRODIGY server. More negative binding energy values indicate stronger and more thermodynamically stable interactions between PDGFR-β and the aptamer structures. Among the analyzed complexes, several aptamers demonstrated highly favorable binding energies, suggesting strong affinity toward the PDGFR-β target and supporting their potential application in Alzheimer's disease diagnostic development.

Table 1. Computer programming: This Python program analyzes a protein sequence from a FASTA file and computes key physicochemical parameters including molecular weight, isoelectric point, net charge, hydrophobicity (GRAVY score), aliphatic index, instability index, and Boman index. It also estimates hydrophobic fraction, amphipathicity, and toxicity potential. These values are normalized and visualized using a radar chart, allowing quick comparison of multiple structural and functional attributes that influence protein solubility, stability, and interaction properties. Such analysis is particularly useful for antibody or therapeutic protein characterization.

Parameter	Formula/Calculation	Biological Significance
Molecular Weight (MW)	MW = Σ(MW_amino_acid) − (n-1) × MW_H2O	Determines protein size, stability, and mobility in SDS-PAGE and chromatography.
Isoelectric Point (pI)	Calculated by finding the pH where Net Charge = 0 using Henderson–Hasselbalch equation: pH = pKa + log([A-]/[HA])	Defines the pH of minimal solubility and used in isoelectric focusing.
Net Charge (at pH 7.4)	Q = Σ(f_basic(pH)) − Σ(f_acidic(pH)), where f is fractional ionization of each ionizable group.	Controls interactions with membranes, DNA, and other proteins.
GRAVY (Grand Average of Hydropathy)	GRAVY = (Σ H_i) / n, where H_i is Kyte–Doolittle hydropathy score.	Positive = hydrophobic, Negative = hydrophilic; impacts folding and solubility.
Hydrophobic Fraction (%)	HF = count(A,I,L,V,F,W,M,Y) / n	Higher hydrophobic content increases membrane affinity and aggregation risk.
Amphipathicity (Hydrophobic Moment, μH)	μH = σ({H_i}), the standard deviation of hydropathy values.	Indicates clustering into hydrophobic vs hydrophilic patches (amphipathic helices).
Aliphatic Index (AI)	AI = X_A + 2.9 X_V + 3.9 (X_I + X_L), where X = mole % of residues.	Correlates with thermostability of proteins.
Instability Index (II)	II = (10/L) × Σ(DIWV(aa_i, aa_{i+1})), where DIWV = dipeptide instability weight.	II < 40 = stable, II > 40 = unstable.
Boman Index (BI)	BI = Σ(s(aa_i)) / n, where s(aa_i) is solubility/interaction potential.	Predicts protein's potential to bind other proteins or molecules.
Toxicity Score	Toxicity = f(charge, hydrophobicity, GRAVY, Boman, etc.). In this script, set as 0.65.	Estimates likelihood of toxic effects based on combined features.

Limitations: One of the main limitations of this research is that it is currently confined to computational analysis, with no experimental validation performed yet. While computational tools provide robust predictions regarding aptamer binding and molecular interactions, they cannot fully replicate the complexity of biological systems. As a result, experimental studies will be essential in the future to confirm the binding efficiency, specificity, and stability of the selected aptamers with PDGFR-β in real biological environments. {Hou, 2013 #1061} Another limitation lies in the use of a limited number of antibodies as reference points or comparative controls. This restricts the ability to bench- mark the performance of the aptamers against a broader range of Ill-characterized binding molecules. A more comprehensive set of antibodies would provide stronger validation for the computational results and help establish the clinical relevance of the selected aptamers. Expanding both the experimental scope and the reference dataset will be crucial steps in advancing this research toward real-world diagnostic applications.

4. CONCLUSION

This study highlights the potential of in silico aptamer design targeting PDGFR-β as a promising strategy for early detection of AD. By integrating structural modeling, binding site prediction, and molecular docking simulations, we identified firm interaction profiles and favorable binding energies that support the feasibility of PDGFR-β as a diagnostic biomarker. The ability to computationally screen aptamers reduces the time and cost of early-phase research, providing a foundation for rapid development of biosensors or diagnostic assays. While experimental validation remains essential to confirm specificity and stability in biological systems, these findings lay the groundwork for aptamer-based diagnostic tools that could enable earlier detection, improve patient outcomes, and complement current AD diagnostic methods.

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