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# CD 34 PRO-ANGIOGENIC TARGET DISCOVERY

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**ABSTRACT:** Cluster of differentiation 34 (CD34) has diverse properties and functions. CD 34 is associated with stem cells. Its roles in angiogenesis and cellular stimulation are well demonstrated. Stem cell and pro-angiogenic therapies are primary rapidly developing fields nowadays. By stimulating CD 34, it is theoretically possible to induce and shape stem cell differentiation. This computational study uses in silico methods applied to some organic molecules that bind to CD34 and presumably stimulate angiogenesis and cell differentiation. Results show that CD 34 is a highly versatile molecule that is probably susceptible to stimulation by small organic molecules.

**Keywords:** CD34, angiogenesis, peripheral artery disease, atherosclerosis, protein-ligand interaction, virtual screening.

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## 1. INTRODUCTION

The CD34 protein is expressed in early hematopoietic and vascular-associated progenitor cells. However, its exact function remains largely unknown. CD34 is a crucial adhesion molecule for T cells entering lymph nodes. It is found on lymph node endothelial, with its binding partner L-selectin on T cells. In different contexts, CD34 has been identified as a molecular "Teflon," preventing mast cell, eosinophil, and dendritic cell precursor adhesion and promoting the opening of vascular lumina. Recent data also suggest a potential selective role for CD34 in the chemokine-dependent migration

of eosinophils and dendritic cell precursors. Regardless of its specific mechanism, CD34 and its counterparts, podocalyxin and endoglycan, consistently facilitate cell migration. Cells that express CD34 (referred to as CD34+ cells) are typically located in the umbilical cord and bone marrow, where they function as hematopoietic cells. They are also present in endothelial progenitor cells, the endothelial cells of blood vessels (excluding lymphatics except for pleural lymphatics), mast cells, and a specific subset of dendritic cells found in the interstitium and around the adnexa of the dermis in the skin[1,2]. Additionally, CD34 is detected in cells within soft tissue tumors such as DFSP, GIST, SFT, HPC, and, to some extent, in MPNSTs. It's noteworthy that Long-Term Hematopoietic Stem Cells (LT-HSCs), which possess significant self-renewal capacity, are identified as CD34+ and CD38− cells within the lineage-depleted cell population (Lin−) in both mice and humans. Human Hematopoietic Stem Cells (HSCs) express the CD34 marker. Subsequent studies have indicated that low rhodamine retention can distinguish LT-HSCs within the Lin−CD34+CD38− population[3,4,5]. CD34+ is frequently utilized in clinical settings to quantify the number of hematopoietic stem cells intended for hematopoietic stem cell transplantation. While it generally serves as a valuable marker for cell dosing, there is some indication that CD34+ quantification may lack reliability in certain situations. The isolation of CD34+ cells from blood samples using immunomagnetic techniques allows for CD34+ transplants, which are associated with lower rates of graft-versus-host disease. Antibodies play a crucial role in quantifying and purifying hematopoietic progenitor stem cells in research and clinical bone marrow transplantation. Consequently, these undifferentiated cells can be sorted based on their CD34+ expression[6,7,8,9,10] CD34 is identified in various tumors, including alveolar soft part sarcoma, preB-ALL (positive in 75%), AML (40%), and AML-M7 (most). A negative CD34 result may exclude Ewing's sarcoma/PNET, myofibrosarcoma of the breast, and inflammatory myofibroblastic tumors of the stomach[11,12,13,14]. Clinically, CD34+ hematopoietic stem cells have been injected to treat conditions like spinal cord injury, liver cirrhosis, and peripheral vascular disease. Standardizing research protocols is crucial for future investigations. Additionally, understanding VEGF isoform profiles in oral tissues is necessary to comprehend their roles better. Targeting molecular mechanisms of angiogenesis, particularly those involving VEGF and its receptors, or using antibodies against VEGF and its receptors may prove beneficial in managing oral cancers. Selective integrin blockade, especially in endothelial cells with heightened expression in tumors, presents a novel anticancer strategy[15,16,17,18]. The mentioned aspect, coupled with the absence of a significant correlation between VEGF and MVD, raises the following points: Some studies propose that as a tumor expands, the overall number of microvessels increases proportionally to the tumor volume, suggesting that MVD is sustained during tumorigenesis. However, currently used markers cannot differentiate between inactive and active endothelial cells, underscoring the necessity for a marker specifically identifying active neoangiogenic vessels. There is also a need for markers to distinguish normal vessels from those within and around tumors[19,20].

In this computational study, the interaction of CD34 with small organic molecules is presented to identify a potent agonist of CD34. This hypothetical interaction must presumably result in CD34 stimulation.]

## 2. MATERIALS AND METHODS

[CD34 Uniprot Aa sequence (UniProt ID P28906 ) was used to generate a homology model. Chembl database was used to curate the ligands used in the virtual screening against the CD34 obtained by homology modeling[21,22]. The homology model was developed using the SwissProt server, and the virtual screening was performed utilizing the VINA software. The presumably hit ligands were selected using an online server for hit property detection along ligands. Docking results and consecutive ligand selection were performed using the complex energy, and the ADME properties of the ligands were determined computationally. The CD34 docking site was determined from the literature data and the online binding site detection server ProBis[23].

## 3. RESULTS AND DISCUSSION

Three cavities were detected: cavity 1 with a volume of 91.648 and a surface of 360.960, and the following cartesian coordinates x 9.18823, y 6.58901, z -32.7558 cavity 2 with a volume of 69.632, a surface of 247.04 and x -19.2667, y 5.18563, z 17.8485 and cavity 3 with a volume of 10.752, a surface of 51.20 with x 2.822, y 7.6212 and z -3.62123. Based on the literature data, surface volume, and ligand accessibility, cavity one was chosen for further studies.

The virtual screening of 1080 molecules against the homology model of CD34 retrieved the following docking total complex energies (Figure 1). As seen in Figure 2 (which represents the total docking energy in detail), only 25 compounds out of 1188 scans can energetically bind effectively to CD 34.

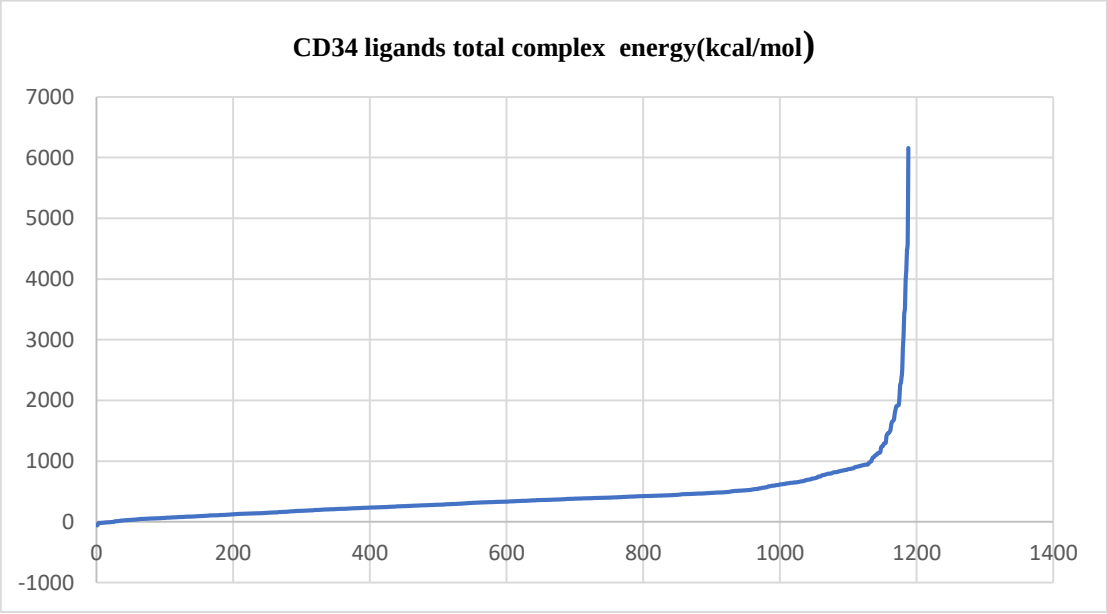


**Figure 1. CD34-ligands total complex energy ( kcal/mol).**

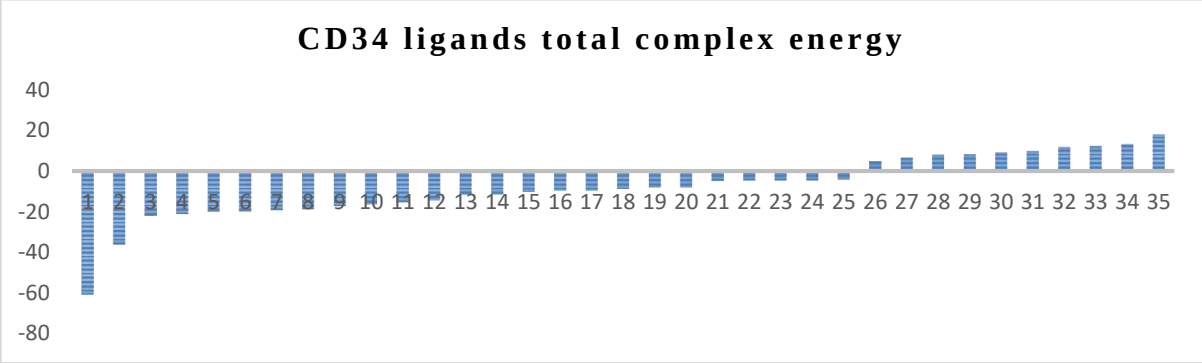


**Figure 2. Detail of CD34-ligands complex energies (kcal/mol).**

In Table 1, the compounds represented in Figure 2 are illustrated. As shown in the figure above, only the first 25 compounds have negative energies (kcal/mol).

**Table 1 structure of the compounds represented in Figure 2**

| | |
|---|---|
| 1 | OC=1C=CC=2OCCC=2C=1 |
| 2 | COC=1C=2C=NC=CC=2ON=1 |
| 3 | O=c1CCC[n]1=C[C][C]=Cn2[cH][cH][cH][cH]2 |
| 4 | BrC(n1)=NC2=[N]=N[CH]C2=[c]1=O |
| 5 | FC([CH]1)=[c](=O)n[C](=O)=[N]1[c]2o[c](C)[c](O)[c]2O |
| 6 | C[N](=CC2=1)C=CC=1ON=C2OC |
| 7 | FC(=C1)c(=O)n[C](=O)=[N]1[c]2oc(=CF)[c](O)[c]2O |
| 8 | BrC=c(o1)[c](O)[c](O)[c]1[N]=2[CH]C(F)=[c](=O)n[C]=2=O |
| 9 | O=c1CCC[n]1=C[C][C]=Cn2[cH][cH][cH][cH]2 |
| 10 | FC([CH]1)=[c](=O)n[C](=O)=[N]1[c]2o[c](C)[c](O)[c]2O |
| 11 | FC([CH]1)=[c](=O)n[C](=O)=[N]1[c]2o[c](C)[c](O)[c]2O |
| 12 | O=c1CCC[n]1=C[C][C]=Cn2[cH][cH][cH][cH]2 |
| 13 | IC=c(o1)[c](O)[c](O)[c]1[N]=2[CH]C(F)=[c](=O)n[C]=2=O |
| 14 | F[C]1C=[NH]C(=O)nc1=O |
| 15 | CN=[C]=1CC2C[CH]C=1C2 |
| 16 | CN=[C]=1CC2C[CH]C=1C2 |
| 17 | FC(=C1)c(=O)n[C](=O)=[N]1[c]2oc(=CF)[c](O)[c]2O |
| 18 | BrC=c(o1)[c](O)[c](O)[c]1[N]=2[CH]C(F)=[c](=O)n[C]=2=O |
| 19 | F[C]1C=[NH]C(=O)nc1=O |
| 20 | BrC=c(o1)[c](O)[c](O)[c]1[N]=2[CH]C(F)=[c](=O)n[C]=2=O |
| 21 | NO[CH]C=CC |
| 22 | FC(=C1)c(=O)n[C](=O)=[N]1[c]2oc(=CF)[c](O)[c]2O |
| 23 | IC=c(o1)[c](O)[c](O)[c]1[N]=2[CH]C(F)=[c](=O)n[C]=2=O |
| 24 | BrC=c(o1)[c](O)[c](O)[c]1[N]=2[CH]C(F)=[c](=O)n[C]=2=O |

| | |
|---|---|
| 25 | C[CH]OC=1C=2C=NC=CC=2ON=1 |
| 26 | F[C](C=1)c(=O)nC(=O)[N]=1[c]2oc(=C[NH3+])[c](O)[c]2O |
| 27 | IC(=CC=1)C=CC=1C=C(N)C |
| 28 | N[C](C)C=C1[CH]C=[CH]=C[CH]1 |
| 29 | NC=1[CH]C(C)=CC=[N]=1 |
| 30 | NC=1[CH]C(C)=CC=[N]=1 |
| 31 | CC1=C(C2)CC=C2C1=NC |
| 32 | IC=c(o1)[c](O)[c](O)[c]1[N]=2[CH]C(F)=[c](=O)n[C]=2=O |
| 33 | BrC=c(o1)[c](O)[c](O)[c]1[N]=2[CH]C(F)=[c](=O)n[C]=2=O |
| 34 | [CH][C]COC=1C=2C=NC=CC=2ON=1 |
| 35 | O=c1[C](O)C(=[C](O[CH]C)=O)C[n]1=C[C]2C=C[CH]C=N2 |

A cluster of the 1188 compound was generated using interaction energies and some molecular descriptors: number of C atoms with sp2 hybridization, number of C atoms with sp3 hybridization, interaction energy of ligand and protein, steric interaction energy, number of heavy atoms, the molecular mass of the ligands, number of N atoms, number of O atoms, number of H atoms, and pose energy respectively. The Cluster is represented in Figure 3. Compounds that show favorable binding with the CD34 protein model are located at the tip of the dome.

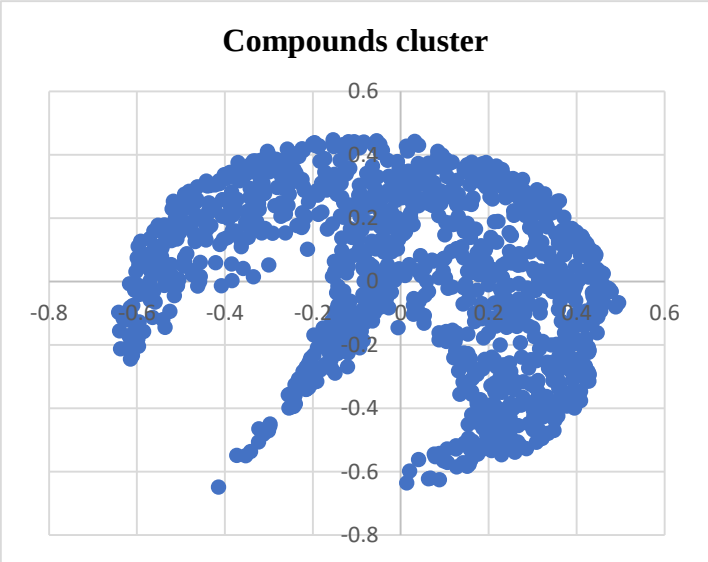


**Figure 3. Property cluster of the 1188 compounds docked against CD34 protein model.**

Cluster of Differentiation 40 (CD40) - a tumor necrosis factor family member, is a promising immune-modulating target in cancer treatment. Physiologically, B cells, myeloid cells, and dendritic cells express CD40, mediating cytotoxic T cell priming via the ligand CD40L. Various approaches, including recombinant CD40L, intratumoral adenoviral vectors, and CD40 antibodies, are being tested in cancer therapy trials, showing safety and promising antitumor effects. Adverse events are manageable. Ongoing studies explore CD40 activation in combination with other treatments, emphasizing the need for predictive biomarkers to identify patients with optimal clinical benefits

[24,25]. Novel azapeptide analogs derived from growth hormone-releasing peptide-6 (GHRP-6) have been crafted as specific CD36 ligands and investigated for their anti-atherosclerotic effects in apoe. Azapeptides MPE-001 and MPE-003 reduced the progression of aortic lesions and lowered lesions in the aortic sinus of atherosclerotic mice, dropping below pre-existing levels. Additionally, there was an observable rise in M2-like macrophages within the lesions and a decrease in systemic inflammation. The development of aza peptides selectively targeting CD36 holds promise for potential interventions in atherosclerotic disease[26,27]. Autosomal Dominant Polycystic Kidney Disease (ADPKD) is an inherited disorder characterized by renal cyst formation due to PKD1 or PKD2 gene mutations. In contrast, the Tuberous Sclerosis Complex (TSC) is an autosomal dominant neurocutaneous syndrome caused by mutations or deletions in the TSC2 gene. A TSC2/PKD1 contiguous gene syndrome results from a chromosomal mutation disrupting TSC2 and PKD1 genes. This syndrome is identified in patients with severe early-onset ADPKD and TSC. Breast cancer patients with the TSC2/PKD1 contiguous gene syndrome exhibit a high mutation burden and produce numerous neoantigens in tumor tissue. Positive immunohistochemistry staining for Cluster of Differentiation 8+ (CD8+) in breast cancer T cells indicates neoantigen production due to the elevated mutation burden[28]. Cluster of Differentiation 36 (CD36) is a cell-surface receptor known for recognizing various substances. Previous evidence hinted at a binding site for lipid ligands within a short segment of the receptor (amino acids 149-168), but direct interaction confirmation was lacking.A fluorescence intensity assay was developed. A synthetic peptide, FITC-CD36149-168, labeled with fluorescein isothiocyanate and variant peptides, served as positive and negative probes. The published results showed specific and saturable binding of 1-palmitoyl-2-(5-keto-6-octenedioyl)phosphatidylcholine (an established CD36 ligand) but not with 1-palmitoyl-2-arachidonyl-phosphatidylcholine. Notably, this assay provided the first evidence of direct and specific binding between the CD36 segment and fatty aldehydes (e.g., Z-11-hexadecenal). However, specific interactions with fatty acids, like oleic acid, were not demonstrated. Nevertheless, these findings contribute to understanding biologically relevant ligands and the role of CD36. The fluorescence-based technique introduced offers a convenient means to assess protein (peptide)-lipid interactions[29]. Recently, immunotherapeutic approaches involving engineered cells and monoclonal antibodies have proven effective in treating various malignancies. This study introduces a synthetic prototype of DNA aptamers designed to activate the T cell receptor cluster of differentiation 3 (TCR-CD3) complex in cultured T cells. The activation potential of these aptamers is comparable to that of a monoclonal antibody against TCR-CD3, suggesting the potential of aptamers in developing effective synthetic immunomodulators. The prototype, targeting TCR-CD3ε, was created using the aptamer ZUCH-1, generated through ligand-guided selection (LIGS). ZUCH-1 was truncated and modified with nuclease-resistant RNA analogs to enhance stability. Dimeric analogs with variable linker lengths were designed, and the optimal activation potential was

observed in a dimeric aptamer with dimensions similar to an antibody. This highlights the importance of optimizing linker lengths in engineering functional aptamers. The study demonstrates the significant potential of aptamers in designing versatile immunomodulators with tunable pharmacokinetic properties, thereby expanding the possibilities of nucleic acid-based ligands like aptamers in immunotherapeutic designs[30]. CD24, a heavily glycosylated mucin-like molecule, has been extensively researched as a cancer stem cell marker across various solid cancers. Its functional role involves interactions with ligands or participation in signal transduction, influencing the initiation and progression of neoplasms. Recently identified as an innate immune checkpoint, CD24 holds significance in several solid cancer types. The summary covers diverse therapeutic agents or strategies targeting CD24 in solid cancers[31]. In subretinal inflammation, activated mononuclear phagocytes (MP) play a crucial role in retinopathy progression, but the mechanism leading to photoreceptor loss and vision impairment is poorly understood. In a study on retinal damage induced by photo-oxidative stress, we found that mice deficient in Cluster of Differentiation 36 (CD36) had reduced subretinal MP accumulation and less severe photoreceptor degeneration.MPE-001 modulated the transcriptome of activated MP, reducing pro-inflammatory markers. In isolated MP, MPE-001 disrupted the CD36-Toll-like receptor 2 (TLR2) complex, inhibiting nuclear factor-kappa B (NF-κB). Additionally, MPE-001 induced an aerobic metabolic shift in activated MP through peroxisome proliferator-activated receptor-γ (PPAR-γ) activation, mitigating inflammation. Inhibition of PPAR-γ blocked the cytoprotective effect of MPE-001 on photoreceptor apoptosis caused by activated MP. By altering MP metabolism, MPE-001 decreased immune responses, alleviating inflammation-dependent neuronal injury in various vision-threatening retinal disorders[32]. Failure to establish immune tolerance can lead to autoimmune diseases, posing a significant challenge in developing strategies to treat them without causing widespread immunosuppression. Another study introduces a translational approach involving the bioengineering of mouse Schwann cells (SCs) with programmed death-ligand 1 (PD-L1) and a cluster of differentiation 86 (CD86) functionality. These engineered SCs, when intravenously administered, alter the disease course and improve experimental autoimmune encephalomyelitis (EAE) in mouse models of multiple sclerosis (MS). The bioengineered SCs inhibit the differentiation of pathogenic T helper type-1 (Th1) and type-17 (Th17) cells, promote tolerogenic myelin-specific regulatory T (Treg) cells, and resolve inflammatory environments in the central nervous system without inducing systemic immunosuppression[33]. Further, in a distinct study from July 2016 to September 2019, 80 patients with suspected coronary heart disease were diagnosed with coronary slow flow (CSF) after angiography at Nanjing Jiangbei People's Hospital. They formed the CSF group, while the normal coronary flow (NCF) group comprised 80 patients with average angiography results. Serum levels of sCD40L and MMP-9 were significantly higher in the CSF group than in the NCF group ($P<0.05$). Adhesion molecules and CRP levels were also elevated

in the CSF group. Positive correlations were found between sCD40L and adhesion molecules in the CSF group and between MMP-9 levels and the corrected TIMI frame count (CTFC). These findings suggest a potential role of chronic inflammation in CSF pathogenesis and the presence of atherosclerotic plaques in CSF patients' coronary arteries. Higher levels of sCD40L, adhesion molecules, and CRP in CSF patients, along with their positive correlation with CTFC, imply a potential role of sCD40L in promoting adhesion molecule expression and contributing to CSF development[34]. The retinal pigment epithelium (RPE) is crucial for maintaining the health of photoreceptors, and oxidative damage to the RPE is a vital factor in diseases like age-related macular degeneration (AMD). Previous studies in mouse AMD models have shown that ligands of Cluster of differentiation 36 (CD36) can preserve photoreceptor integrity. In a recent study using human RPE cells subjected to oxidative stress induced by sodium iodate (NaIO3), the CD36 ligand MPE-001 demonstrated a protective effect. MPE-001 reduced both reactive oxygen species and apoptosis without affecting the transcription of antioxidant enzymes. Furthermore, MPE-001 restored disrupted autophagic flux caused by NaIO3, leading to the formation of mature autophagosomes. This autophagy-dependent protection was nullified when autophagy inhibitors wortmannin and bafilomycin A1 were introduced. This study unveils, for the first time, the protective role of autophagy mediated by a CD36 ligand in shielding RPE cells from oxidative stress[35]

## 4. CONCLUSION

CD34 is a versatile protein. The virtual screening proved that small organic molecules can effectively bind to CD34-specific binding sites. Also, the CD34 binding site seems difficult to access, while 25 out of 1188 ligands formed energetically favorable complexes with CD34. Lastly, further in silico studies with expensive ligand libraries and the refinement of the CD34 homology model are required to successfully asses a hit.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

## HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

## CONSENT FOR PUBLICATION

Not applicable.

## FUNDING

None.

## CONFLICT OF INTEREST

There are no conflicts of interest.

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