Structural Insight into the Dual Ligand Specificity and Mode of High Density Lipoprotein Association of Apolipoprotein D**

Human apolipoprotein D (ApoD) occurs in plasma associated with high density lipoprotein. Apart from the involvement in lipid metabolism, its binding activity for progesterone and arachidonic acid plays a role in cancer development and neuropsychiatric disorders. The crystal structures of free ApoD and its complex with progesterone were determined at 1.8 Å resolution and reveal a lipocalin fold. The narrow, mainly uncharged pocket within the typical β-barrel accommodates progesterone with its acetyl side chain oriented toward the bottom. The cavity adopts essentially the same shape in the absence of progesterone and allows complexation of arachidonic acid as another cognate ligand. Three of the four extended loops at the open end of the β-barrel expose hydrophobic side chains, which is an unusual feature for lipocalins and probably effects association with the high density lipoprotein particle by mediating insertion into the lipid phase. This mechanism is in line with an unpaired Cys residue in the same surface region that can form a disulfide cross-link with apolipoprotein A-II.

In addition, ApoD is synthesized by astrocytes in the central nervous system (11), and there, it seems to be involved in arachidonic acid transport, metabolism, and signaling (12). Notably, ApoD plays a well documented pathophysiological role in several psychiatric disorders (12), especially in schizophrenia (13).

ApoD has been prepared as a soluble recombinant protein via secretion into the periplasm of *Escherichia coli*, and its binding activity for progesterone and arachidonic acid, both with $K_D$ values around 1 μM, was demonstrated (14). However, recombinant ApoD reveals a pronounced tendency to adsorb to surfaces and to form aggregates upon storage, which may be explained by hydrophobic surface properties that enable ApoD to interact with HDL and/or with lipid membranes in its physiological environment. Using systematic substitution of presumably exposed hydrophobic residues, we were able to construct a “solubilized” mutant of ApoD that retained native ligand binding function and appeared to be suitable for structural analysis (15).

**EXPERIMENTAL PROCEDURES**

*Protein Production and Crystallization*—An engineered version of ApoD was produced in *E. coli* via periplasmic secretion essentially as described (15). As mass spectrometric analysis revealed some inhomogeneity with respect to the processing of the N-terminal OmpA signal peptide, the first 2 residues of the mature protein sequence, Gln-Ala, were deleted from the expression plasmid via site-directed mutagenesis, yielding pApoD27ΔQA. Seleno-l-methionine-labeled protein was subsequently prepared according to a published protocol (16). The recombinant protein was purified by immobilized metal affinity chromatography and gel filtration on an analytical Superdex 75 column in the presence of 100 mM NaCl, 1 mM EDTA, 10 mM Tris/HCl, pH 8.0.

For crystallization, the protein was dialyzed against the same buffer without EDTA and concentrated to 15 mg/ml using 10-kDa cut-off Vivaspin tubes (Sartorius AG, Hannover, Germany) followed by sterile filtration with 0.45-μm Spin-X centrifuge tube filters (Corning Inc., Corning, NY). Crystals were grown at 20 °C as described (15), using micro-seeding and refined conditions of 1.1 M Li$_2$SO$_4$, 100 mM NH$_4$HCO$_3$, 75 mM Hepes/NaOH, pH 7.5, soaked in the precipitant solution supplemented with 30% (v/v) glycerol and flash-frozen in liquid nitrogen. The ApoD–progesterone complex was prepared by soaking crystals of the seleno-l-methionine-labeled protein for 48 h in the precipitant solution containing ~4 μM progesterone (minimum 99%, Sigma-Aldrich).

*Data Collection and Processing*—For structure solution of the uncomplexed ApoD by multiple wavelength anomalous dispersion (MAD), three data sets were collected from a sin-
complex with progesterone, even some more residues (Phe-3–Thr-34, Gly-39–Glu-50, Gly-54–Asp-106). The electron density map of the uncomplexed ApoD allowed model building of the uncomplexed ApoD using REFMAC (17). The electron density map of the uncomplexed ApoD was built using the MAD phasing (18). Three selenium atom sites were identified with SHELX (18). The electron density map of the uncomplexed ApoD was calculated from the refined structure of the uncomplexed ApoD-progesterone complex. A single wavelength data set was collected at beam line ID14-4 of the European Synchrotron Radiation Facility (ESRF) (Grenoble, France). Diffraction data up to a resolution of 1.80 Å were measured at 100 K (Table 1), processed with MOSFLM, scaled with SCALA, and reduced with TRUNCATE (17). The structure of the ApoD-arachidonate complex was modeled with the program O and idealized with REFMAC. The coordinates for the free ApoD and its complex with progesterone have been deposited at the Protein Data Bank (PDB codes 2HZR and 2HZQ).

**RESULTS**

**Tertiary Structure of ApoD**—The crystal structure of human ApoD reveals an eight-stranded, antiparallel β-barrel flanked by an α-helix (Fig. 1), as it is typical for the lipocalin protein family (31). The calyx has an outer diameter of around 45 Å at its broadest site and a length of around 40 Å. Four loops connect the β-strands A/B, C/D, E/F, and G/H (Fig. 1A) in a pairwise fashion and thus form the entrance to the characteristic ligand-binding site of the lipocalins. In the case of ApoD, the narrow, conically shaped, and mainly hydrophobic cavity is ~15 Å deep and about 10 by 15 Å wide at its entry (Fig. 1B).

The N-terminal peptide segment runs across the bottom of the β-barrel between the two short loops that connect strands B/C and F/G, respectively, before it enters into β-strand A. A short 310-helix (Val-19–Lys-21) forms a cap that closes the β-barrel (Fig. 1A). The Cys residues 8 and 114 as well as 41 and 165 form two disulfide bridges (4). The first disulfide bond connects the N-terminal segment to strand G of the β-barrel, whereas the second one fixes the C terminus to strand B. Thus, the connectivity is similar to the bilin-binding protein (BBP; Fig. 2), a structurally well characterized lipocalin from the butterfly *Pieris brassicae* (32), but it differs from the retinol-binding protein (RBP), another abundant human plasma lipocalin (31). In fact, a weak sequence homology between ApoD and BBP was noted before (33).

### Table 1

| Data set                | Peak        | Inflection point | Remote | Ligand complex |
|-------------------------|-------------|-----------------|--------|----------------|
| Space group             | P4₂,2,2     |                 |        |                |
| Unit cell dimensions    |             |                 |        |                |
| a, b, c [Å], α = β = γ = 90° | 49.25, 49.25, 143.49 | 49.37, 49.37, 144.05 | 49.41, 49.41, 144.12 | 49.21, 49.21, 144.13 |
| Wavelength [Å]          | 0.97940     | 0.97969         | 0.96863 | 1.00890        |
| Resolution range [Å]   | 30.00–1.80 (1.90–1.80) 30.00–2.00 (2.11–2.00) 30.00–2.30 (2.42–2.30) 30.00–1.80 (1.90–1.80) | 6.4 (2.2) | 8.1 (2.2) | 7.9 (2.1) | 6.6 (2.3) |
| Rmerge [%]              | 6.7 (28.5)  | 6.0 (22.8)      | 7.3 (36.0) | 7.0 (30.8)     |
| Unique reflections      | 17002       | 12649           | 8486   | 17084          |
| Multiplicity            | 15.0        | 13.4            | 13.2   | 11.3           |
| Completeness            | 99.1 (98.7)| 99.4 (99.2)     | 99.6 (99.5) | 98.7 (95.3) |
| Anomalous completeness  | 99.5 (98.7)| 99.8 (99.5)     | 99.9 (99.7) |                |

**Phasing and refinement**

| Figure of merit         | 0.410       |                      |        |                |
| Rmerge/Rfree            | 20.24/24.98 | 18.68/22.58          |        |                |
| Protein atoms           | 1284        | 1318               |        |                |
| Ligand atoms            | 23          | 23                 |        |                |
| Solvent atoms           | 152         | 235                |        |                |
| Average B-factor [Å²]   | 22.82       | 22.55              |        |                |

**Ramachandran analysis**

| Core, allowed, generously allowed [%] | 91.4, 6.5, 2.2 | 90.2, 8.4, 1.4 |

**Values in parentheses are for the highest resolution shell.**

3 W. L. DeLano, PyMOL.
The crystal structure of human ApoD in complex with progesterone. A, side view of the lipocalin β-barrel with the characteristic α-helix in the back. Secondary structure is depicted in yellow (β-strands), green (coils), and pink (α-helix as well as 3-10-helix), respectively, whereas the two disulfide bridges are shown in orange. Loops A/B, C/D, E/F, and G/H at the open end of the β-barrel are highlighted in cyan and labeled. The bound progesterone is shown as a stick model (gray, with the two oxygen atoms colored red). The mutated side chains of His-99, Ser-116, Ser-118, and Ser-120 in the solubilized ApoD (15) are shown as sticks in light blue. The mutated residues Pro-23, Val-133, and Ala-134, which were introduced to facilitate protein engineering (42), are colored in dark gray, whereas the two N-linked glycosylation sites Asn-45 and Asn-78 of the native protein are shown in dark blue. The position of the disordered residue Glu-50 (at the bottom) is marked in light gray. B, view from the top into the opening of the β-barrel with the bound ligand. C, detailed view of progesterone bound in the ligand pocket of ApoD (carbon, light orange; oxygen, pink; nitrogen, cyan), together with its 2Fo − Fc electron density contoured at 0.8 σ. The side chains of Phe-89 and Trp-127, which sandwich the steroid molecule, are labeled, together with three Tyr side chains in the vicinity. The hydrogen bond between the keto oxygen at C20 of progesterone and Tyr-22 OH (acceptor-donor distance 2.6 Å) is indicated by a red dashed line, whereas the hydrogen-bonding network between the hydroxyl groups of Tyr-46, Tyr-98, and Tyr-22 are represented by pink dashed lines (acceptor-donor distances of 2.7 and 2.8 Å, respectively). D, comparison between the crystal structures of free ApoD (yellow) and of its complex with progesterone (red). Residues 35–38 (corresponding to loop A/B) and 51 in the apo-structure and residue 50 in the holo-structure, which are not defined in the electron density map, are omitted. Residues that contact progesterone in the complex with ApoD are shown as sticks in lighter colors. Only two of the contacting side chains, Asn-58 and Tyr-46, exhibit different side chain conformations.

The four largely exposed loops at the open top of the β-barrel shape the ligand cavity of ApoD. There, two opposite pairs of β-strands, which support the loops C/D and G/H, are bent widely open, thus granting access to the binding site. Both loops form hairpin turns (residues Arg-62–Thr-66 and Ile-117–Ser-120, respectively). The two other loops, which connect β-strands A/B and E/F (Ile-32–Gly-39 and Phe-89–Ser-95, respectively), are substantially longer, with an Ω-type appearance for loop A/B. Three of these loops form protrusions and expose bulky hydrophobic side chains (see below), e.g. loop A/B with Phe-36, loop E/F with Trp-91 and Phe-92, and loop G/H with Phe-121, which is also in vicinity of the hydrophobic N-terminal residue Phe-3.

The two tight loops C/D and G/H are involved in altogether eight hydrogen bonds with four symmetry-related molecules. Arg-62 NH2 in loop C/D forms a hydrogen bond to Glu-138 OE1 in the first turn of the α-helix, close to the bottom of the β-barrel, of the first neighboring molecule. The adjacent residue Glu-60 forms with its carbonyl oxygen two hydrogen bonds via water molecules to the second symmetry-related molecule, one to Ser-116 O in strand G and the second one to Ser-118 N in the loop G/H. Residue Gly-65 forms with its carbonyl oxygen a hydrogen bond to Ser-120 OG in loop G/H of the third neighboring molecule. The corresponding donor/acceptor groups of the residues Ser-116, Ser-118, and Glu-138 in the original molecule form symmetrical hydrogen bonds to the crystallographic neighbors numbers one and two, whereas Ser-120 OG forms a hydrogen bond to Gly-65 O in loop C/D of the fourth neighboring molecule. As the residues that are involved in these interactions lie at the tip of the two loops, except for Glu-138 in the α-helix, and are thus all remote from the central cavity, it seems unlikely that ligand binding is influenced by crystal-packing contacts.

The ligand pocket of ApoD is lined by mainly hydrophobic side chains (in particular, Tyr-22, Trp-26, Tyr-46, Ile-54, Tyr-98, Val-111, Trp-127, and Leu-129; Fig. 1D), which explains its binding activity for the non-polar ligand progesterone (see below) and also for arachidonic acid (14). Residues Tyr-46 and Tyr-98 form the bottom of the ligand pocket. Together with Tyr-22, they are arranged like a trigonal pyramid, whereby their side chain hydroxyl groups form a hydrogen bond network (Fig. 1C).

The ligand pocket is slightly negatively charged due to residue Glu-60 close to its entrance. Residues Glu-28 and Lys-31 in β-strand A form a salt bridge (length: 2.6 Å). In the apo-form of the protein, the side chain oxygen atom of Asn-58 forms a hydrogen bond with the hydroxyl group of Tyr-46, which is mediated by a water molecule. This water molecule is absent in the complex structure due to a conformational change of the Asn-58 side chain. In the apo-structure, there are altogether 13 ordered water molecules in the upper part of the cavity, which are arranged in typical hydrogen-bonding distances.

The Complex with Progesterone—The crystal structures of free ApoD and its complex with progesterone are almost identical, with an r.m.s.d. of just 0.38 Å upon superposition of the Cα positions 3–34, 39–50, and 52–168 (Fig. 1D). The only differences are some conformational changes of the side chains of Asn-45, Asn-58, and Tyr-46. Progesterone is deeply buried in the cleft, with the A-ring of the steroid system oriented toward...
the entrance. The steroid molecule is sandwiched between the aromatic side chains of Phe-89 and Trp-127 such that the two methyl groups (C18 and C19) point toward residue Phe-89 (Fig. 1C). A hydrogen bond is formed between the keto oxygen of the aromatic side chains of Phe-89 and Trp-127 such that the two C–C double bonds from steroid ring A to B. These structural changes occur in a region that is close to the entrance of the ligand pocket of ApoD where the packing with protein side chains is less tight.

Pairwise superposition of all 21 carbon atoms of progesterone in the ApoD structure with the crystal structure of progesterone alone (CCDC accession number KEF-BEC) (34) led to an r.m.s.d. of 0.16 Å. In contrast, the same pairwise superposition of pregnenolone (CCDC: PREGOL) with progesterone in the ApoD structure led to a significantly larger r.m.s.d. of 0.33 Å, whereby major deviations occurred around C4, C6, and for the substituent at C3. According to this superposition, the carbon atoms C6 and C7 of pregnenolone would make significantly closer contacts (by ~0.6 Å) to Trp-127 of ApoD (cf. Fig. 1C).

**Structural Comparison with Other Lipocalins**—A search for homologous protein structures in the Protein Data Bank using DALI (35) revealed that ApoD is most closely related to insect BBP (PDB accession number 1BBP; Z-score = 20.4) (32) followed by the crustacyanin subunit A1 (PDB: 1H91; Z-score = 19.1) (36)

The bacterial lipocalin of *E. coli* (PDB: 1QWD; Z-score = 17.5) (37) as well as porcine RBP (PDB: 1AQB; Z-score = 16.2) (38) showed less similarity. Interestingly, insectocytochrome (39) showed detectable sequence similarity with ApoD (33), but did not show up in this DALI search.

Superposition of the ApoD and BBP crystal structures, as complexes with their cognate ligands progesterone and biliverdin IXₐ, respectively, using the structurally conserved set of 58 Cαatoms of the β-barrel (31), led to an r.m.s.d. of 0.96 Å (Fig. 3). Despite the remarkable similarity of the tertiary structures of these two phylogenetically distant lipocalins, there are signifi-

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**TABLE 2. Structure-based amino acid alignment between the crystallized recombinant ApoD, the human wild type protein (NCBI GenInfo Identifier, GI:619383), and BBP from *P. brassicae* (cabbage butterfly; GI:229695; PDB: 1BBP).**

Sequences of orthologous proteins from various species are shown below the figure. Secondary structure elements were deduced from the ApoD crystal structure using DSSP (24) and are depicted as arrows (for β-strands; labeled β if part of the β-barrel) or cylinder (for the C-terminal α-helix). β-Barrel residues that are structurally conserved among the prototypic lipocalins (31) are highlighted by a yellow background. The bacterial lipocalin of *E. coli* (PDB: 1QWD; Z-score = 17.5) (37) as well as porcine RBP (PDB: 1AQB; Z-score = 16.2) (38) showed less similarity. Interestingly, insectocytochrome (39), another insect lipocalin with similar ligand binding function as the BBP from *P. brassicae* (40), showed less similarity. Interestingly, insecticyanin (39), another insect lipocalin with similar ligand binding function as the BBP from *P. brassicae* (40), showed less similarity.
Crystal Structure of Human ApoD-Progesterone

A side view in stereo with the ligand-binding sites at the top. ApoD is colored in shades of red, and BBP (PDB: 1BBP, chain A) is colored in shades of blue. The structurally conserved β-barrel segments (cf. Fig. 2) are shown in darker colors, respectively. The disulfide bonds are shown as orange (ApoD) and green (BBP) sticks. The bound ligands are depicted as stick models in violet (progesterone for ApoD) and cyan (biliverdin IXα, for BBP). B, pairwise Cα atom distances between the crystal structures of ApoD and BBP according to the sequence alignment shown in Fig. 2 and after superposition of the structurally conserved β-barrel residues highlighted therein (r.m.s.d. of 0.96 Å for 58 Cα positions). Missing graph segments correspond to gaps in the sequence alignment.

The pronounced similarity between the β-barrel structures of ApoD and BBP becomes further evident from an analysis of the interior residue packing within its lower part. There, 26 amino acids whose side chains protrude from the strands and the bottom loops connect the neighboring antiparallel strands at both ends of the β-barrel (cf. Figs. 2 and 3). At the bottom, two of the three loops have identical lengths, whereas loop B/C is longer by one residue in ApoD. Notably, at the open end of the β-barrel, where the ligand-binding site is situated, all four loops have a different length in ApoD when compared with BBP (A/B, −1; C/D, +1; E/F, −2; G/H, −1). Furthermore, there are significant conformational differences in the loop region at the entrance to the ligand pocket as mentioned above.

Despite these mutual deviations in the variable loop region, which are typical for the lipocalin family (31), the β-barrel is extremely well conserved between ApoD and BBP (Fig. 3A). This varying similarity in main chain conformation also becomes apparent from an r.m.s.d. plot (Fig. 3B). In particular, the conserved lipocalin sequence motif GXWX, which occurs within the N-terminal loop that runs across the bottom of the β-barrel before it enters into strand A (residues 24–27), is conformationally almost identical between the two crystal structures, except that the solvent-exposed side chain at position 27 corresponds to a Tyr in ApoD and to a Trp in BBP.

Role of “Solubilizing” Amino Acid Substitutions—In a preceding protein engineering study (15), 4 amino acid exchanges were introduced at the surface of ApoD (W99H, C116S, I118S, and G124S) to increase solubility, which led to a 3-fold increase in the expression level of ApoD. In this study, 10 conservative substitutions (15) were made in the remaining solubility-enhancing mutants, 5 of which were identical with BBP. These were W99H, G124D, R125H, M126T, and E128D. Notably, the conservation pattern(ies) of the lipocalin family was reflected by the sequence similarity of 85% in this region is much higher than with other lipocalins. For example, there are just 9 amino acid identities between ApoD and human plasma RBP (PDB: 1RBP) (41) within this set, together with ~10 conservative substitutions. This finding illustrates the unusual structural relationship between human ApoD and the insect BBP despite their large evolutionary distance.
L120S) to enhance the solubility of the recombinant protein and another three (L23P, P133V, N134A) were introduced to facilitate its genetic manipulation (42) (Fig. 1A). At all of these sites, the polypeptide backbone conformation seems not to be influenced by the side chain substitutions also because residues in equivalent positions of the BBP are located very close to those of ApoD in the superimposed structures (Fig. 3A). In fact, the mutations introduced into human ApoD were all correctly predicted as pointing with their side chains into the solvent. Since there is no mutation inside the cavity, the binding activity for small molecules should not be affected, which is in agreement with biochemical data for the engineered protein (15).

Notably, only one of the replaced side chains, Ser-120, is directly involved in crystal-packing contacts. It forms a hydrogen bond between its OG atom and the backbone oxygen of Gly-65 of a neighboring molecule. Another 2 substituted residues, Ser-116, and Ser-118, form intermolecular hydrogen bonds via their main chain atoms, as explained above. Together with the generally enhanced solubility due to the side chain replacements (15), these specific interactions may have contributed to the successful crystallization of the engineered ApoD.

Considering its occurrence as a soluble protein, native ApoD possesses an unusually strong hydrophobic character (Fig. 4). The solvent-accessible surface of all Ile, Leu, Met, Phe, Trp, Tyr, and Val residues (including main chain atoms) on the outside of the modeled wild type protein (with side chains back-mutated in favorable geometry) adds up to 2593 Å². A considerable fraction of the solvent-accessible surface of 408 Å² is contributed by the 7 mutated residues in the engineered version. Two large hydrophobic patches around loops G/H and E/F, which come together on one face of ApoD (Fig. 4B), were clearly made more hydrophilic by this mutagenesis.

The unpaired Cys-116, which is responsible for covalent cross-link to ApoA-II in the HDL particle and was replaced by Ser in the recombinant protein, is also located in this region. Thus, the present crystal structure supports the hypothesis that the prominent hydrophobic surface region promotes initial association of ApoD with the lipid phase of HDL prior to formation of the disulfide bond with ApoA-II. A non-covalent hydrophobic association may even be sufficient for its physiological role in lipid metabolism because Cys-116 is missing in all other vertebrate species for which the ApoD sequence is known to date (cf. Fig. 2).

**DISCUSSION**

The crystal structure of ApoD reveals an eight-stranded antiparallel β-barrel that is typical for the lipocalin protein family. However, ApoD exhibits distinctive features that were not yet observed for other lipocalins. First, ApoD pos-
The prominent hydrophobic patches on the surface of ApoD are located in the area that surrounds the ligand pocket (Fig. 4). It is conceivable that the apolar side chains act as molecular protrusions that insert into the lipid phase of the HDL particle before the disulfide cross-link with Cys-6 of Apo-AII (43) gets formed. This structural feature of ApoD may also help to take up (or release) the hydrophobic ligand from the lipid disc. Elevated B-factors for the loop regions indicate the required flexibility for such an interaction. The orientation of ApoD would then appear as a cup with its opening pointing toward the HDL particle and its back forming a spike that may even be available for interaction with an as yet unknown cellular receptor (44).

Apart from its occurrence as HDL-associated plasma protein, human ApoD is found in other body liquids and tissues, especially in the brain. There, its physiological function seems to lie mainly in the transport of arachidonate, whose metabolism is closely linked to neurological disorders (12). Indeed, the cavity of ApoD as it appears from the crystal structure, both in the presence and in the absence of progesterone, is perfectly shaped to accommodate this unsaturated fatty acid as well. Arachidonate can be modeled with a bent all-cis configuration into the protein pocket. Most of the protein residues that would contact the hydrocarbon part of the ligand are of hydrophobic nature (Ile-42, Ala-44, Ile-70, Val-87, Phe-89, Ala-96, Trp-127, Leu-129), whereas its carboxylic group could form a hydrogen bond to the carboxamide side chain of Asn-68 (Fig. 5).

Several disease-causing mutations in the APOD gene have been described. Three mutations are potentially linked to cardiovascular disease among African populations: F36V, Y108C, and T158K (45). However, none of these mutations are located within the cavity such that the ligand binding activity of ApoD should not be directly affected. Mutation F36V in loop A/B causes an exchange of a large exposed hydrophobic side chain to a smaller one. This alters the proposed interface of ApoD and could influence its docking to the HDL particle. Indeed, this allele was associated among females with significantly decreased levels of ApoA-I and of cholesterol in the denser HDL3 subfraction. Mutation Y108C is located at the closed end of the β-barrel in β-strand G, i.e. within the same strand as the Cys residues 114 and 116, which give rise to an intramolecular disulfide bridge of ApoD and to the cross-link with ApoA-II, respectively. Thus, the additional Cys residue is likely to cause non-physiological disulfide bonds during oxidative folding of ApoD and may lead to a loss of function. The mutation T158K occurs in the extended C-terminal polypeptide segment, which wraps partly around the β-barrel, in close proximity to Lys-31. Electrostatic repulsion might lead to subtle effects on the shape of the ligand pocket. Further genetic analyses describe single nucleotide polymorphisms that are linked to Alzheimer disease (46) or to schizophrenia (47, 48), either via a mutation in the signal peptide or by influencing mRNA processing.

In conclusion, the elucidation of the tertiary structure of ApoD again demonstrates the broad variability and adaptivity of lipocalin family members. Its detailed atomic structure should allow the guided selection of antagonistic ligands that may be useful for the treatment of plasma lipid disorders or prevent the binding and transport of arachidonate, thus yielding potential drugs for the therapy of psychiatric disorders (12). Finally, knowledge of the ApoD crystal structure should also boost the development of artificial lipocalins with novel binding activities, so-called anticalins (31, 42, 49).
Crystal Structure of Human ApoD-Progesterone

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