Table 1. Overview of studies which have identified plasma proteins that Cd^{2+} can interact with/bind to. Top-down (TD) refers to studies in which Cd^{2+} was added to plasma (P)/serum (S) and bottom-up (BU) refers to studies in which Cd^{2+} was added to pure proteins and binding was observed. All information in rows 3-4 was obtained from the first reference in that row unless otherwise indicated. Values for stability constants and serum/plasma concentrations have been converted into K_d and μM, respectively.

Protein/Metalloprotein **• Size (kDa)** **◦ Plasma/Serum Concentration**	**TD (S/P) /BU**	**Technique(s) used**	**• Protein identification** **◦ Binding information**	**• Other relevant details** **◦ Protein structure**
α_2-Macroglobulin[1] (α_2M) • 725 kDa ◦ 1.52 – 4.28 μM$^{(M)}$[2] ◦ 1.93 – 5.06 μM$^{(W)}$[2]	BU	Cd^{2+}-incubated samples of 74% pure α_2M in 0.1 M Tris* buffer (pH 7.4) were applied to a SEC* column and collected fractions were analyzed for Cd^{2+} using AAS*.	◦ 4[#] binding sites and K_d (K_d = 9.6 x 10^{-7} M)[3]	• Number of Cd^{2+} binding sites was confirmed in a subsequent study.[3] • 2D-IEP and ^{109}Cd radiolabeling was used to demonstrate Cd^{2+} binding to α_2M in serum.[4] ◦ PDB: 4ACQ
Apolipoprotein A-I[5] • 30.8 kDa ◦ 36.6 – 44.8 μM[6]	TD (P)	Plasma samples (n = 29) containing 0.08 ± 0.07 ng/mL Cd^{2+} from natural exposure of the blood donors was used. Following the removal of serum albumin and immunoglobulin G from the plasma, Cd^{2+}-binding proteins were separated using a Mini Prep Cell column GE apparatus (Bio-Rad). The resulting eluent was split, with half being analyzed by ICP-MS* for Cd^{2+} and the other Cd-containing fractions were concentrated for subsequent protein identification. A single cadmium-binding protein was detected in the samples.	• After 1D page analysis and staining, the Cd-binding protein was manually excised and qualitatively identified by MS/MS after trypsin-digestion.	◦ PDB: 1AV1
Apolipoprotein B-100[7] • 497 kDa ◦ 2.07 ± 0.48 μM$^{(M)}$[8] ◦ 1.93 ± 0.52 μM$^{(W)}$[8]	TD (S)	After loading serum onto a Cd-loaded IMAC* column, the latter was washed with 20 mM BTS buffer* and bound proteins were eluted with 0.1 M EDTA*.	• The eluted proteins underwent trypsin digestion and were identified by LC-MS/MS*.	-
Ceruloplasmin[7] • 132 kDa ◦ 1.52 – 3.03 μM[9]	TD (S)	see above.	• see above.	◦ PDB: 1KCW
Hemopexin[7] 57.0 kDa ◦ 8.77 – 17.5 μM[10]	TD (S)	see above.	• see above.	-
Histidine-rich glycoprotein[11] (HRG) • 75.0 kDa ◦ 1.33 – 2.00 μM[12]	BU	A HRG-heme complex (10 heme:1 HRG) exhibits a characteristic UV absorption spectrum. Incubation of HRG dissolved in 0.1 M phosphate buffer (pH 7.1) with $CdCl_2$ (1 HRG: 20 $CdCl_2$) followed by the addition of heme (1 HRG:10 heme) resulted in a decreased absorption band at 414 nm compared to the HRG-heme control, indicating that Cd^{2+} obstructed the binding of heme to HRG.	◦ Evidence that a Gly-His-His-Pro-His motif, which is repeated 12 times in the amino acid sequence of HRG, is responsible for heme and divalent metal ion binding (including Cd^{2+}).[13]	• Confirmation of the HRG repeat motif.[13]
Immunoglobulin A[4] • 160 kDa ◦ 6.25 – 18.8 μM[14]	TD (S)	Serum proteins were separated by 2D-IEP*. Incubation of the gel with radioactive metal (^{109}Cd) species followed by the exposure of gel to X-ray film revealed Cd-binding proteins.	• Proteins were identified using serum which contained monospecific antibodies.	◦ PDB: 2QTJ
Immunoglobulin G[4] • 150 kDa ◦ 80.0 – 100 μM[15]	TD (S)	see above.	• see above.	◦ PDB: 1HZH
Prealbumin (Transthyretin)[4] • 55.0 kDa ◦ 5.45 – 6.00 μM$^{(M)}$[16] ◦ 4.55 – 4.91 μM$^{(W)}$[16]	TD (S)	see above.	• see above.	◦ PDB: 1BMZ

Human serum albumin[17] (HSA) (HSA) • 66.5 kDa ◦ 526 – 752 μM[18]	BU + TD (S)	Pure HSA (2 mM) in 0.1 M phosphate buffer (pH 7.0) in D_2O was titrated with 20 – 100 mM solutions of $CdCl_2$ using ^{113}Cd and ^{1}H NMR* spectroscopy. Finally, whole serum was titrated with Cd^{2+} and analyzed by ^{113}Cd-NMR spectroscopy.	◦ Results indicate that Cd^{2+} binds to sites A and B with similar affinity.[17] ◦ 2 strong binding sites A+B[17], (K_d = 5 x 10^{-6} M)[19] ◦ 1 weak binding site[19] ◦ Evidence provided that Cd^{2+}-binding site A is comprised of His67, His247, Asn99, and Asp249.[20]	• A BU experiment which used SEC in conjunction with PBS-buffer demonstrated that 0.5 mM D,L-homocysteine mobilizes Cd^{2+} from HSA, which is relevant to hyperhomocysteinemia.[21] • A BU equilibrium dialysis study investigated the binding of Cd^{2+} to HRG as a Cd-binding protein in competition with HSA. HRG was able to bind Cd^{2+} with higher affinity than HSA, but the binding is less relevant because of the comparatively lower HRG concentration. [22] • A BU study using circular dichroism and electron spin resonance spectroscopy in 0.15 M NaCl (pH 7.4) demonstrated the displacement of Cu^{2+} by Cd^{2+} from it's second strongest binding site in HSA.[23] ◦ PDB: 1AO6
Transferrin[24] • 80.0 kDa ◦ 22.3 – 44.3 μM[(M)][2] ◦ 22.5 – 46.5 μM[(W)][2]	BU	Differences in the UV spectra (240 – 320 nm) of apo-transferrin were recorded after titration with $CdCl_2$ solution. Protein was dissolved in 10 mM Hepes*, 5 mM sodium bicarbonate at pH 7.4.	◦ Cd^{2+} has a greater affinity for the C- than the N-terminal site.[24] ◦ C-terminal: K_d = 1.1 x 10^{-6} M[24] ◦ N-terminal: K_d = 1.4 x 10^{-5} M[24]	• ^{13}C and ^{113}Cd NMR spectroscopy were used to confirm the presence of one His binding residue in Cd-transferrin complexes.[25] • ^{113}Cd NMR spectroscopy revealed differences in the binding of Cd^{2+} to the N- and C-lobe.[26] ◦ PDB: 2HAV

***Technique and Reagent Acronyms**: Size-exclusion chromatography (SEC); Atomic absorption spectroscopy (AAS); Gel Electrophoresis (GE); Gel Electrophoresis Inductively-coupled plasma mass spectrometry (GE-ICP-MS); Immobilized metal affinity chromatography (IMAC); Liquid chromatography (LC); 2-D Immunoelectrophoresis (2D-IEP); Nuclear magnetic resonance (NMR); 2-Amino-2-(hydroxymethyl)propane-1,3-diol (Tris); bis-Tris Saline (BTS); Ethylenediaminetetraacetic acid (EDTA); 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (Hepes).

[#]Evidence suggests that a single Cd^{2+} ion will bind each of the 4 monomer subunits.

[(M)]The concentration range provided refers to levels in men.

[(W)]The concentration range provided refers to levels in women.