Electronic Supplementary Material (ESI) for Nanoscale.


# Nanoparticles-cell association predicted by protein corona fingerprints

Sara Palchetti,[a,b] Luca Digiacomo,[a,c] Daniela Pozzi,[a,b] Giovanna Peruzzi,[d] Elisa Micarelli,[e] Morteza Mahmoudi[f,g*] and Giulio Caracciolo[a,b*]

[a]*Department of Molecular Medicine, "Sapienza" University of Rome, Viale Regina Elena 291, 00161 Rome, Italy.*

[b]*Istituti Fisioterapici Ospitalieri, Istituto Regina Elena, Via Elio Chianesi 53, 00144 Rome, Italy.*

[c]*School of Biosciences and Veterinary Medicine, University of Camerino, Via Gentile III da Varano, 62032 Camerino (MC), Italy.*

[d]*Istituto Italiano di Tecnologia, CLNS@Sapienza, Viale Regina Elena 291, 00161, Rome, Italy*
[e]*Department of Biology, University of Rome Tor Vergata, Via della Ricerca Scientifica 1, 00133 Rome, Italy.*

[f]*Nanotechnology Research Center, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran.*

[g]*Department of Anesthesiology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA*

*(GC) E-mail: giulio.caracciolo@uniroma1.it; (MM) E-mail: mmahmoudi@bwh.harvard.edu

**Table S1.** Cell viability (%) and cell association (%) of the different nanoparticles used valuated by flow cytometry as percentage of fluorescent cells. Date are average values of three independent experiments ± standard deviation. Adapted with permission from [A. Bigdeli, S. Palchetti, D. Pozzi, M. R. Hormozi-Nezhad, F. Baldelli Bombelli, G. Caracciolo and M. Mahmoudi, ACS nano, 2016, 10, 3723-3737].

| | Cell viability (%) | Cell association (%) |
|---|---|---|
| NP1 | 86±9 | 98.3±0.2 |
| NP2 | 91±1 | 99.85±0.07 |
| NP3 | 93±8 | 95±3 |
| NP4 | 84±4 | 99.9±0.9 |
| NP5 | 78±1 | 97±4 |
| NP6 | 96±2 | 68±4 |
| NP7 | 89±1 | 88.4±0.4 |
| NP8 | 92±6 | 64±10 |
| NP9 | 90±8 | 2.1±0.4 |
| NP10 | 93±6 | 0.5±0.2 |
| NP11 | 89±7 | 0.84±0.03 |
| NP12 | 79±2 | 0.7±0.3 |
| NP13 | 89±5 | 89±4 |
| NP14 | 77±2 | 98.1±0.6 |
| NP15 | 100±4 | 87±2 |
| NP16 | 79±3 | 61±1 |

**Table S2.** Total number of identified proteins on the different nanoparticles used.

| | Number of identified proteins |
|---|---|
| NP1 | 219 |
| NP2 | 191 |
| NP3 | 167 |
| NP4 | 134 |
| NP5 | 189 |
| NP6 | 205 |
| NP7 | 205 |
| NP8 | 198 |
| NP9 | 182 |
| NP10 | 166 |
| NP11 | 175 |
| NP12 | 153 |
| NP13 | 202 |
| NP14 | 261 |
| NP15 | 239 |
| NP16 | 239 |

**Table S3-S18.** Top 25 most abundant corona proteins identified in the protein corona of nanoparticles NP2-NP16 following 1 hour incubation with HP. Common proteins are highlighted in gray.

| # | NP 2 - Top 25 | Accession Number | RPA (%) | St. Dev. (%) |
|---|---|---|---|---|
| 1 | Apolipoprotein C-III | APOC3 | 16.80 | 0.42 |
| 2 | Vitronectin | VTNC | 8.93 | 0.22 |
| 3 | Serum albumin | ALBU | 8.56 | 0.21 |
| 4 | Clusterin | CLUS | 3.75 | 0.09 |
| 5 | Apolipoprotein C-II | APOC2 | 3.24 | 0.08 |
| 6 | Apolipoprotein A-I | APOA1 | 2.01 | 0.05 |
| 7 | Hemoglobin subunit alpha | HBA | 1.74 | 0.04 |
| 8 | Apolipoprotein D | APOD | 1.69 | 0.04 |
| 9 | Thymosin beta-4 | TYB4 | 1.63 | 0.04 |
| 10 | Ig gamma-1 chain C region | IGHG1 | 1.56 | 0.04 |
| 11 | Apolipoprotein A-IV | APOA4 | 1.44 | 0.04 |
| 12 | Serum paraoxonase/arylesterase 1 | PON1 | 1.42 | 0.04 |
| 13 | Actin, cytoplasmic 2 | ACTG | 1.39 | 0.03 |
| 14 | Ig kappa chain C region | IGKC | 1.38 | 0.03 |
| 15 | Hemoglobin subunit beta | HBB | 1.33 | 0.03 |
| 16 | Fibrinogen beta chain | FIBB | 1.32 | 0.03 |
| 17 | Alpha-1-antitrypsin | A1AT | 1.28 | 0.03 |
| 18 | Apolipoprotein E | APOE | 1.21 | 0.03 |
| 19 | Complement C3 | CO3 | 1.16 | 0.03 |
| 20 | Prothrombin | THRB | 1.13 | 0.03 |
| 21 | Serum amyloid A protein | SAA | 1.11 | 0.03 |
| 22 | Ig gamma-2 chain C region | IGHG2 | 1.09 | 0.03 |
| 23 | Ig lambda-2 chain C regions | LAC2 | 1.00 | 0.02 |
| 24 | Profilin-1 | PROF1 | 0.98 | 0.02 |
| 25 | Fibrinogen gamma chain | FIBG | 0.96 | 0.02 |

| # | NP 3 - Top 25 | Accession Number | RPA (%) | St. Dev. (%) |
|---|---|---|---|---|
| 1 | Complement C4-B | CO4B | 5.48 | 0.14 |
| 2 | Serum albumin | ALBU | 4.66 | 0.12 |
| 3 | Inter-alpha-trypsin inhibitor heavy chain H2 | ITIH2 | 4.49 | 0.11 |
| 4 | Prothrombin | THRB | 4.13 | 0.10 |
| 5 | Ig gamma-1 chain C region | IGHG1 | 4.06 | 0.10 |
| 6 | Fibrinogen beta chain | FIBB | 3.99 | 0.10 |
| 7 | Vitamin K-dependent protein S | PROS | 3.73 | 0.09 |
| 8 | Ig kappa chain C region | IGKC | 3.68 | 0.09 |
| 9 | C4b-binding protein alpha chain | C4BPA | 3.24 | 0.08 |
| 10 | Vitronectin | VTNC | 2.94 | 0.07 |
| 11 | Apolipoprotein A-I | APOA1 | 2.87 | 0.07 |
| 12 | Inter-alpha-trypsin inhibitor heavy chain H1 | ITIH1 | 2.50 | 0.06 |
| 13 | Ig gamma-3 chain C region | IGHG3 | 2.46 | 0.06 |
| 14 | Complement C3 | CO3 | 2.39 | 0.06 |
| 15 | Inter-alpha-trypsin inhibitor heavy chain H3 | ITIH3 | 2.30 | 0.06 |
| 16 | Fibrinogen gamma chain | FIBG | 2.14 | 0.05 |
| 17 | Protein AMBP | AMBP | 1.84 | 0.05 |
| 18 | Ig gamma-2 chain C region | IGHG2 | 1.80 | 0.05 |
| 19 | Fibrinogen alpha chain | FIBA | 1.61 | 0.04 |
| 20 | Ig lambda-2 chain C regions | LAC2 | 1.59 | 0.04 |
| 21 | Vitamin K-dependent protein Z | PROZ | 1.40 | 0.04 |
| 22 | Protein Z-dependent protease inhibitor | ZPI | 1.25 | 0.03 |
| 23 | Apolipoprotein A-II | APOA2 | 1.01 | 0.03 |
| 24 | Apolipoprotein E | APOE | 0.95 | 0.02 |
| 25 | Vitamin K-dependent protein C | PROC | 0.93 | 0.02 |

| # | NP 4 - Top 25 | Accession Number | RPA (%) | St. Dev. (%) |
|---|---|---|---|---|
| 1 | Serum albumin | ALBU | 5.55 | 0.14 |
| 2 | Apolipoprotein A-I | APOA1 | 4.09 | 0.10 |
| 3 | Apolipoprotein C-III | APOC3 | 3.10 | 0.08 |
| 4 | Apolipoprotein A-II | APOA2 | 2.97 | 0.07 |
| 5 | Apolipoprotein C-II | APOC2 | 2.85 | 0.07 |
| 6 | Hemoglobin subunit beta | HBB | 2.81 | 0.07 |
| 7 | Apolipoprotein C-I | APOC1 | 2.73 | 0.07 |
| 8 | Apolipoprotein D | APOD | 2.73 | 0.07 |
| 9 | Apolipoprotein E | APOE | 2.69 | 0.07 |
| 10 | Keratin, type II cytoskeletal 1 | K2C1 | 2.56 | 0.06 |
| 11 | Actin, cytoplasmic 1 | ACTB | 2.50 | 0.06 |
| 12 | Ig kappa chain C region | IGKC | 2.39 | 0.06 |
| 13 | Complement C3 | CO3 | 2.30 | 0.06 |
| 14 | Ig lambda-2 chain C regions | LAC2 | 2.23 | 0.06 |
| 15 | Keratin, type I cytoskeletal 10 | K1C10 | 2.08 | 0.05 |
| 16 | Fibrinogen gamma chain | FIBG | 1.94 | 0.05 |
| 17 | Ig gamma-1 chain C region | IGHG1 | 1.86 | 0.05 |
| 18 | Vitronectin | VTNC | 1.79 | 0.04 |
| 19 | Hemoglobin subunit alpha | HBA | 1.73 | 0.04 |
| 20 | Keratin, type I cytoskeletal 9 | K1C9 | 1.69 | 0.04 |
| 21 | Apolipoprotein B-100 | APOB | 1.61 | 0.04 |
| 22 | Keratin, type II cytoskeletal 2 epidermal | K22E | 1.59 | 0.04 |
| 23 | Fibrinogen beta chain | FIBB | 1.58 | 0.04 |
| 24 | Alpha-1-antitrypsin | A1AT | 1.33 | 0.03 |
| 25 | Apolipoprotein A-IV | APOA4 | 1.24 | 0.03 |

| # | NP 5 - Top 25 | Accession Number | RPA (%) | St. Dev. (%) |
|---|---|---|---|---|
| 1 | Serum albumin | ALBU | 4.63 | 0.12 |
| 2 | Ig kappa chain C region | IGKC | 4.23 | 0.11 |
| 3 | Fibrinogen beta chain | FIBB | 4.21 | 0.11 |
| 4 | Apolipoprotein A-I | APOA1 | 3.26 | 0.08 |
| 5 | Ig gamma-1 chain C region | IGHG1 | 3.13 | 0.08 |
| 6 | Prothrombin | THRB | 2.97 | 0.07 |
| 7 | Inter-alpha-trypsin inhibitor heavy chain H2 | ITIH2 | 2.62 | 0.07 |
| 8 | Vitronectin | VTNC | 2.55 | 0.06 |
| 9 | Fibrinogen gamma chain | FIBG | 2.33 | 0.06 |
| 10 | Complement C3 | CO3 | 2.30 | 0.06 |
| 11 | Ig gamma-2 chain C region | IGHG2 | 2.15 | 0.05 |
| 12 | Complement C4-B | CO4B | 2.09 | 0.05 |
| 13 | Ig gamma-3 chain C region | IGHG3 | 1.91 | 0.05 |
| 14 | Fibrinogen alpha chain | FIBA | 1.87 | 0.05 |
| 15 | Vitamin K-dependent protein S | PROS | 1.87 | 0.05 |
| 16 | Inter-alpha-trypsin inhibitor heavy chain H3 | ITIH3 | 1.75 | 0.04 |
| 17 | Inter-alpha-trypsin inhibitor heavy chain H1 | ITIH1 | 1.71 | 0.04 |
| 18 | C4b-binding protein alpha chain | C4BPA | 1.63 | 0.04 |
| 19 | Clusterin | CLUS | 1.61 | 0.04 |
| 20 | Alpha-1-antitrypsin | A1AT | 1.51 | 0.04 |
| 21 | Apolipoprotein A-IV | APOA4 | 1.42 | 0.04 |
| 22 | Vitamin K-dependent protein Z | PROZ | 1.28 | 0.03 |
| 23 | Kininogen-1 | KNG1 | 1.26 | 0.03 |
| 24 | Apolipoprotein E | APOE | 1.19 | 0.03 |
| 25 | Serum paraoxonase/arylesterase 1 | PON1 | 1.12 | 0.03 |

| # | NP 6 - Top 25 | Accession Number | RPA (%) | St. Dev. (%) |
|---|---|---|---|---|
| 1 | Ig kappa chain C region | IGKC | 7.79 | 0.19 |
| 2 | Prothrombin | THRB | 7.73 | 0.19 |
| 3 | Inter-alpha-trypsin inhibitor heavy chain H1 | ITIH1 | 5.08 | 0.13 |
| 4 | C4b-binding protein alpha chain | C4BPA | 3.43 | 0.09 |
| 5 | Inter-alpha-trypsin inhibitor heavy chain H2 | ITIH2 | 3.01 | 0.08 |
| 6 | Fibrinogen beta chain | FIBB | 2.92 | 0.07 |
| 7 | Vitronectin | VTNC | 2.73 | 0.07 |
| 8 | Ig lambda-2 chain C regions | LAC2 | 2.26 | 0.06 |
| 9 | Ig gamma-1 chain C region | IGHG1 | 2.19 | 0.05 |
| 10 | Protein AMBP | AMBP | 2.19 | 0.05 |
| 11 | Complement C4-B | CO4B | 2.09 | 0.05 |
| 12 | Vitamin K-dependent protein S | PROS | 1.98 | 0.05 |
| 13 | Ig mu chain C region | IGHM | 1.94 | 0.05 |
| 14 | Serum albumin | ALBU | 1.91 | 0.05 |
| 15 | Serum paraoxonase/arylesterase 1 | PON1 | 1.74 | 0.04 |
| 16 | Fibrinogen gamma chain | FIBG | 1.58 | 0.04 |
| 17 | Complement C3 | CO3 | 1.34 | 0.03 |
| 18 | Ig gamma-3 chain C region | IGHG3 | 1.20 | 0.03 |
| 19 | Apolipoprotein E | APOE | 1.13 | 0.03 |
| 20 | Inter-alpha-trypsin inhibitor heavy chain H3 | ITIH3 | 1.10 | 0.03 |
| 21 | Ig gamma-4 chain C region | IGHG4 | 1.04 | 0.03 |
| 22 | Hyaluronan-binding protein 2 | HABP2 | 1.03 | 0.03 |
| 23 | Apolipoprotein A-I | APOA1 | 1.00 | 0.02 |
| 24 | Fibrinogen alpha chain | FIBA | 0.99 | 0.02 |
| 25 | Ceruloplasmin | CERU | 0.96 | 0.02 |

| # | NP 7 - Top 25 | Accession Number | RPA (%) | St. Dev. (%) |
|---|---|---|---|---|
| 1 | Prothrombin | THRB | 8.33 | 0.21 |
| 2 | Ig kappa chain C region | IGKC | 5.58 | 0.14 |
| 3 | Inter-alpha-trypsin inhibitor heavy chain H1 | ITIH1 | 5.16 | 0.13 |
| 4 | Inter-alpha-trypsin inhibitor heavy chain H2 | ITIH2 | 3.76 | 0.09 |
| 5 | C4b-binding protein alpha chain | C4BPA | 3.53 | 0.09 |
| 6 | Protein AMBP | AMBP | 3.10 | 0.08 |
| 7 | Vitronectin | VTNC | 2.98 | 0.07 |
| 8 | Fibrinogen beta chain | FIBB | 2.36 | 0.06 |
| 9 | Serum albumin | ALBU | 2.24 | 0.06 |
| 10 | Ig mu chain C region | IGHM | 2.03 | 0.05 |
| 11 | Ig lambda-2 chain C regions | LAC2 | 2.01 | 0.05 |
| 12 | Ig mu heavy chain disease protein | MUCB | 1.85 | 0.05 |
| 13 | Fibrinogen gamma chain | FIBG | 1.70 | 0.04 |
| 14 | Ig gamma-1 chain C region | IGHG1 | 1.69 | 0.04 |
| 15 | Complement C4-B | CO4B | 1.60 | 0.04 |
| 16 | Vitamin K-dependent protein S | PROS | 1.55 | 0.04 |
| 17 | Complement C3 | CO3 | 1.50 | 0.04 |
| 18 | Hyaluronan-binding protein 2 | HABP2 | 1.50 | 0.04 |
| 19 | Inter-alpha-trypsin inhibitor heavy chain H3 | ITIH3 | 1.46 | 0.04 |
| 20 | Serum paraoxonase/arylesterase 1 | PON1 | 1.25 | 0.03 |
| 21 | Clusterin | CLUS | 1.19 | 0.03 |
| 22 | Apolipoprotein A-I | APOA1 | 1.13 | 0.03 |
| 23 | Apolipoprotein C-III | APOC3 | 1.10 | 0.03 |
| 24 | Apolipoprotein E | APOE | 1.02 | 0.03 |
| 25 | Ig gamma-3 chain C region | IGHG3 | 1.00 | 0.03 |

| # | NP 8 - Top 25 | Accession Number | RPA (%) | St. Dev. (%) |
|---|---|---|---|---|
| 1 | Prothrombin | THRB | 7.62 | 0.19 |
| 2 | Ig kappa chain C region | IGKC | 5.81 | 0.15 |
| 3 | Inter-alpha-trypsin inhibitor heavy chain H1 | ITIH1 | 4.40 | 0.11 |
| 4 | Inter-alpha-trypsin inhibitor heavy chain H2 | ITIH2 | 3.36 | 0.08 |
| 5 | C4b-binding protein alpha chain | C4BPA | 3.28 | 0.08 |
| 6 | Protein AMBP | AMBP | 2.94 | 0.07 |
| 7 | Vitronectin | VTNC | 2.79 | 0.07 |
| 8 | Serum albumin | ALBU | 2.67 | 0.07 |
| 9 | Ig mu chain C region | IGHM | 2.27 | 0.06 |
| 10 | Ig lambda-2 chain C regions | LAC2 | 2.20 | 0.05 |
| 11 | Ig mu heavy chain disease protein | MUCB | 2.05 | 0.05 |
| 12 | Complement C4-B | CO4B | 1.70 | 0.04 |
| 13 | Fibrinogen beta chain | FIBB | 1.69 | 0.04 |
| 14 | Ig gamma-1 chain C region | IGHG1 | 1.62 | 0.04 |
| 15 | Hyaluronan-binding protein 2 | HABP2 | 1.50 | 0.04 |
| 16 | Serum paraoxonase/arylesterase 1 | PON1 | 1.49 | 0.04 |
| 17 | Complement C3 | CO3 | 1.48 | 0.04 |
| 18 | Apolipoprotein E | APOE | 1.45 | 0.04 |
| 19 | Inter-alpha-trypsin inhibitor heavy chain H3 | ITIH3 | 1.41 | 0.04 |
| 20 | Clusterin | CLUS | 1.34 | 0.03 |
| 21 | Fibrinogen gamma chain | FIBG | 1.32 | 0.03 |
| 22 | Vitamin K-dependent protein S | PROS | 1.26 | 0.03 |
| 23 | Apolipoprotein C-III | APOC3 | 1.14 | 0.03 |
| 24 | Complement C1q subcomponent subunit B | C1QB | 1.03 | 0.03 |
| 25 | Complement C1q subcomponent subunit A | C1QA | 1.03 | 0.03 |

| # | NP 9 - Top 25 | Accession Number | RPA (%) | St. Dev. (%) |
|---|---|---|---|---|
| 1 | Ig kappa chain C region | IGKC | 9.12 | 0.23 |
| 2 | Serum albumin | ALBU | 5.59 | 0.14 |
| 3 | Complement C3 | CO3 | 4.29 | 0.11 |
| 4 | Ig mu chain C region | IGHM | 3.38 | 0.08 |
| 5 | Ig lambda-2 chain C regions | LAC2 | 2.77 | 0.07 |
| 6 | C4b-binding protein alpha chain | C4BPA | 2.15 | 0.05 |
| 7 | Apolipoprotein A-I | APOA1 | 2.04 | 0.05 |
| 8 | Ig gamma-1 chain C region | IGHG1 | 1.98 | 0.05 |
| 9 | Inter-alpha-trypsin inhibitor heavy chain H1 | ITIH1 | 1.82 | 0.05 |
| 10 | Fibrinogen beta chain | FIBB | 1.70 | 0.04 |
| 11 | Prothrombin | THRB | 1.59 | 0.04 |
| 12 | Complement factor H | CFAH | 1.49 | 0.04 |
| 13 | Inter-alpha-trypsin inhibitor heavy chain H2 | ITIH2 | 1.43 | 0.04 |
| 14 | Apolipoprotein C-III | APOC3 | 1.37 | 0.03 |
| 15 | Ig gamma-3 chain C region | IGHG3 | 1.33 | 0.03 |
| 16 | Complement C4-B | CO4B | 1.32 | 0.03 |
| 17 | Apolipoprotein B-100 | APOB | 1.27 | 0.03 |
| 18 | Complement C4-A | CO4A | 1.27 | 0.03 |
| 19 | Ig gamma-4 chain C region | IGHG4 | 1.26 | 0.03 |
| 20 | Complement C1q subcomponent subunit B | C1QB | 1.19 | 0.03 |
| 21 | Immunoglobulin lambda-like polypeptide 5 | IGLL5 | 1.14 | 0.03 |
| 22 | Ceruloplasmin | CERU | 1.14 | 0.03 |
| 23 | Ig gamma-2 chain C region | IGHG2 | 1.13 | 0.03 |
| 24 | Protein AMBP | AMBP | 1.10 | 0.03 |
| 25 | Fibrinogen gamma chain | FIBG | 1.10 | 0.03 |

| # | NP 10 - Top 25 | Accession Number | RPA (%) | St. Dev. (%) |
|---|---|---|---|---|
| 1 | Ig kappa chain C region | IGKC | 10.79 | 0.27 |
| 2 | Serum albumin | ALBU | 7.25 | 0.18 |
| 3 | Complement C3 | CO3 | 3.46 | 0.09 |
| 4 | Ig mu chain C region | IGHM | 2.74 | 0.07 |
| 5 | Ig lambda-2 chain C regions | LAC2 | 2.59 | 0.06 |
| 6 | Ig gamma-1 chain C region | IGHG1 | 2.35 | 0.06 |
| 7 | Ig gamma-3 chain C region | IGHG3 | 2.27 | 0.06 |
| 8 | Ig mu heavy chain disease protein | MUCB | 2.22 | 0.06 |
| 9 | Fibrinogen beta chain | FIBB | 2.18 | 0.05 |
| 10 | C4b-binding protein alpha chain | C4BPA | 2.14 | 0.05 |
| 11 | Complement C1q subcomponent subunit B | C1QB | 2.12 | 0.05 |
| 12 | Apolipoprotein A-I | APOA1 | 1.92 | 0.05 |
| 13 | Ig gamma-2 chain C region | IGHG2 | 1.81 | 0.05 |
| 14 | Apolipoprotein C-III | APOC3 | 1.72 | 0.04 |
| 15 | Complement C1q subcomponent subunit A | C1QA | 1.55 | 0.04 |
| 16 | Apolipoprotein A-II | APOA2 | 1.42 | 0.04 |
| 17 | Apolipoprotein E | APOE | 1.42 | 0.04 |
| 18 | Fibrinogen gamma chain | FIBG | 1.34 | 0.03 |
| 19 | Keratin, type II cytoskeletal 1 | K2C1 | 1.31 | 0.03 |
| 20 | Complement factor H | CFAH | 1.27 | 0.03 |
| 21 | Complement C4-B | CO4B | 1.11 | 0.03 |
| 22 | Serotransferrin | TRFE | 1.04 | 0.03 |
| 23 | Alpha-1-antitrypsin | A1AT | 1.04 | 0.03 |
| 24 | Complement C4-A | CO4A | 1.04 | 0.03 |
| 25 | Keratin, type I cytoskeletal 10 | K1C10 | 1.01 | 0.03 |

| # | NP 11 - Top 25 | Accession Number | RPA (%) | St. Dev. (%) |
|---|---|---|---|---|
| 1 | Fibrinogen beta chain | FIBB | 6.33 | 0.24 |
| 2 | Serum albumin | ALBU | 5.81 | 0.21 |
| 3 | Beta-2-glycoprotein 1 | APOH | 4.40 | 0.04 |
| 4 | Fibrinogen gamma chain | FIBG | 4.12 | 0.36 |
| 5 | Ig kappa chain C region | IGKC | 3.45 | 0.34 |
| 6 | Apolipoprotein C-III | APOC3 | 3.44 | 0.21 |
| 7 | Fibrinogen alpha chain | FIBA | 3.24 | 0.31 |
| 8 | Keratin, type I cytoskeletal 10 | K1C10 | 3.23 | 0.18 |
| 9 | Keratin, type II cytoskeletal 1 | K2C1 | 2.85 | 0.07 |
| 10 | Keratin, type II cytoskeletal 2 epidermal | K22E | 2.58 | 0.05 |
| 11 | Keratin, type I cytoskeletal 9 | K1C9 | 1.96 | 0.05 |
| 12 | Alpha-2-HS-glycoprotein | FETUA | 1.81 | 0.08 |
| 13 | Apolipoprotein A-II | APOA2 | 1.77 | 0.21 |
| 14 | Clusterin | CLUS | 1.68 | 0.06 |
| 15 | Ig lambda-2 chain C regions | LAC2 | 1.63 | 0.21 |
| 16 | Ig gamma-1 chain C region | IGHG1 | 1.42 | 0.18 |
| 17 | Complement C3 | CO3 | 1.39 | 0.03 |
| 18 | OS=Homo sapiens GN=IGHG3 PE=1 SV=2 | IGHG3 | 1.24 | 0.13 |
| 19 | Ig gamma-2 chain C region | IGHG2 | 1.21 | 0.23 |
| 20 | Serum paraoxonase/arylesterase 1 | PON1 | 1.19 | 0.14 |
| 21 | Apolipoprotein A-I | APOA1 | 1.12 | 0.10 |
| 22 | Apolipoprotein E | APOE | 1.09 | 0.07 |
| 23 | C4b-binding protein alpha chain | C4BPA | 1.07 | 0.10 |
| 24 | Apolipoprotein A-IV | APOA4 | 1.02 | 0.07 |
| 25 | Ig mu chain C region | IGHM | 1.00 | 0.05 |

| # | NP 12 - Top 25 | Accession Number | RPA (%) | St. Dev. (%) |
|---|---|---|---|---|
| 1 | Fibrinogen beta chain | FIBB | 5.78 | 0.27 |
| 2 | Fibrinogen alpha chain | FIBA | 4.48 | 0.12 |
| 3 | Fibrinogen gamma chain | FIBG | 4.09 | 0.19 |
| 4 | Histidine-rich glycoprotein | HRG | 3.66 | 0.22 |
| 5 | Clusterin | CLUS | 3.34 | 0.24 |
| 6 | Keratin, type II cytoskeletal 1 | K2C1 | 3.14 | 0.11 |
| 7 | Keratin, type I cytoskeletal 9 | K1C9 | 3.13 | 0.17 |
| 8 | Serum albumin | ALBU | 2.98 | 0.27 |
| 9 | Ig kappa chain C region | IGKC | 2.67 | 0.41 |
| 10 | Apolipoprotein C-III | APOC3 | 2.49 | 0.12 |
| 11 | Keratin, type I cytoskeletal 10 | K1C10 | 2.33 | 0.20 |
| 12 | Keratin, type II cytoskeletal 2 epidermal | K22E | 2.21 | 0.02 |
| 13 | Kininogen-1 | KNG1 | 2.01 | 0.02 |
| 14 | Vitronectin | VTNC | 2.00 | 0.13 |
| 15 | Ig lambda-2 chain C regions | LAC2 | 1.85 | 0.12 |
| 16 | Transthyretin | TTHY | 1.81 | 0.08 |
| 17 | Inter-alpha-trypsin inhibitor heavy chain H4 | ITIH4 | 1.66 | 0.12 |
| 18 | Gelsolin | GELS | 1.48 | 0.06 |
| 19 | Serum paraoxonase/arylesterase 1 | PON1 | 1.47 | 0.16 |
| 20 | Ig mu chain C region | IGHM | 1.42 | 0.10 |
| 21 | Complement C3 | CO3 | 1.41 | 0.08 |
| 22 | Serum amyloid A-1 protein | SAA1 | 1.40 | 0.10 |
| 23 | Actin, cytoplasmic 1 | ACTB | 1.15 | 0.06 |
| 24 | Apolipoprotein A-II | APOA2 | 1.14 | 0.12 |
| 25 | Apolipoprotein A-IV | APOA4 | 1.13 | 0.15 |

| # | NP 13 - Top 25 | Accession Number | RPA (%) | St. Dev. (%) |
|---|---|---|---|---|
| 1 | Apolipoprotein C-II | APOC2 | 2.61 | 0.07 |
| 2 | Apolipoprotein E | APOE | 2.57 | 0.06 |
| 3 | Apolipoprotein A-I | APOA1 | 2.53 | 0.06 |
| 4 | Apolipoprotein C-III | APOC3 | 2.22 | 0.06 |
| 5 | Apolipoprotein A-IV | APOA4 | 2.03 | 0.05 |
| 6 | Complement C3 | CO3 | 1.69 | 0.04 |
| 7 | Apolipoprotein C-I | APOC1 | 1.65 | 0.04 |
| 8 | Keratin, type II cytoskeletal 1 | K2C1 | 1.62 | 0.04 |
| 9 | OS=Homo sapiens GN=APOA2 PE=1 SV=1 | APOA2 | 1.54 | 0.04 |
| 10 | Tropomyosin alpha-4 chain | TPM4 | 1.54 | 0.04 |
| 11 | Fibrinogen beta chain | FIBB | 1.54 | 0.04 |
| 12 | Prothrombin | THRB | 1.47 | 0.04 |
| 13 | Complement C4-B | CO4B | 1.40 | 0.04 |
| 14 | Hemoglobin subunit beta | HBB | 1.33 | 0.03 |
| 15 | Ig kappa chain C region | IGKC | 1.33 | 0.03 |
| 16 | Serum albumin | ALBU | 1.31 | 0.03 |
| 17 | Ig kappa chain V-III region HAH | KV312 | 1.29 | 0.03 |
| 18 | Inter-alpha-trypsin inhibitor heavy chain H2 | ITIH2 | 1.28 | 0.03 |
| 19 | Transthyretin | TTHY | 1.26 | 0.03 |
| 20 | Ig lambda-2 chain C regions | LAC2 | 1.25 | 0.03 |
| 21 | Clusterin | CLUS | 1.25 | 0.03 |
| 22 | Vitronectin | VTNC | 1.24 | 0.03 |
| 23 | Fibrinogen gamma chain | FIBG | 1.22 | 0.03 |
| 24 | Keratin, type I cytoskeletal 9 | K1C9 | 1.18 | 0.03 |
| 25 | Fibrinogen alpha chain | FIBA | 1.17 | 0.03 |

| # | NP 14 - Top 25 | Accession Number | RPA (%) | St. Dev. (%) |
|---|---|---|---|---|
| 1 | Apolipoprotein A-I | APOA1 | 2.47 | 0.06 |
| 2 | Apolipoprotein C-II | APOC2 | 2.24 | 0.06 |
| 3 | Apolipoprotein C-III | APOC3 | 2.24 | 0.06 |
| 4 | Apolipoprotein A-IV | APOA4 | 1.89 | 0.05 |
| 5 | Apolipoprotein E | APOE | 1.87 | 0.05 |
| 6 | Keratin, type II cytoskeletal 1 | K2C1 | 1.71 | 0.04 |
| 7 | Complement C3 | CO3 | 1.69 | 0.04 |
| 8 | Ig kappa chain C region | IGKC | 1.56 | 0.04 |
| 9 | Hemoglobin subunit beta | HBB | 1.54 | 0.04 |
| 10 | Apolipoprotein C-I | APOC1 | 1.42 | 0.04 |
| 11 | Apolipoprotein A-II | APOA2 | 1.39 | 0.03 |
| 12 | Keratin, type I cytoskeletal 10 | K1C10 | 1.31 | 0.03 |
| 13 | Keratin, type II cytoskeletal 2 epidermal | K22E | 1.30 | 0.03 |
| 14 | Serum albumin | ALBU | 1.28 | 0.03 |
| 15 | Keratin, type I cytoskeletal 9 | K1C9 | 1.28 | 0.03 |
| 16 | Ig lambda-2 chain C regions | LAC2 | 1.24 | 0.03 |
| 17 | Actin, cytoplasmic 1 | ACTB | 1.19 | 0.03 |
| 18 | Complement C4-B | CO4B | 1.11 | 0.03 |
| 19 | Fibrinogen beta chain | FIBB | 1.08 | 0.03 |
| 20 | Ig kappa chain V-III region HAH | KV312 | 1.03 | 0.03 |
| 21 | Ig mu chain C region | IGHM | 1.02 | 0.03 |
| 22 | Profilin-1 | PROF1 | 1.02 | 0.03 |
| 23 | Thymosin beta-4 | TYB4 | 1.02 | 0.03 |
| 24 | Inter-alpha-trypsin inhibitor heavy chain H2 | ITIH2 | 1.01 | 0.03 |
| 25 | Alpha-1-antitrypsin | A1AT | 1.00 | 0.02 |

| # | NP 15 - Top 25 | Accession Number | RPA (%) | St. Dev. (%) |
|---|---|---|---|---|
| 1 | Ig kappa chain C region | IGKC | 5.79 | 0.14 |
| 2 | Complement C3 | CO3 | 5.21 | 0.13 |
| 3 | Ig lambda-2 chain C regions | LAC2 | 3.42 | 0.09 |
| 4 | Apolipoprotein C-III | APOC3 | 3.14 | 0.08 |
| 5 | Complement C1q subcomponent subunit A | C1QA | 2.58 | 0.06 |
| 6 | Serum albumin | ALBU | 2.46 | 0.06 |
| 7 | Ig mu chain C region | IGHM | 2.40 | 0.06 |
| 8 | Apolipoprotein E | APOE | 1.95 | 0.05 |
| 9 | Complement C1q subcomponent subunit B | C1QB | 1.79 | 0.04 |
| 10 | Complement C4-B | CO4B | 1.69 | 0.04 |
| 11 | Apolipoprotein A-I | APOA1 | 1.66 | 0.04 |
| 12 | Keratin, type II cytoskeletal 1 | K2C1 | 1.47 | 0.04 |
| 13 | Apolipoprotein A-II | APOA2 | 1.47 | 0.04 |
| 14 | Apolipoprotein C-II | APOC2 | 1.31 | 0.03 |
| 15 | Alpha-1-antitrypsin | A1AT | 1.22 | 0.03 |
| 16 | Hemoglobin subunit alpha | HBA | 1.22 | 0.03 |
| 17 | Keratin, type I cytoskeletal 10 | K1C10 | 1.22 | 0.03 |
| 18 | Hemoglobin subunit beta | HBB | 1.19 | 0.03 |
| 19 | Keratin, type I cytoskeletal 9 | K1C9 | 1.17 | 0.03 |
| 20 | Complement C1q subcomponent subunit C | C1QC | 1.17 | 0.03 |
| 21 | Apolipoprotein A-IV | APOA4 | 1.16 | 0.03 |
| 22 | Ig gamma-1 chain C region | IGHG1 | 1.12 | 0.03 |
| 23 | Ig kappa chain V-III region HAH | KV312 | 1.10 | 0.03 |
| 24 | Keratin, type II cytoskeletal 2 epidermal | K22E | 1.08 | 0.03 |
| 25 | Fibrinogen beta chain | FIBB | 1.07 | 0.03 |

| # | NP 16 - Top 25 | Accession Number | RPA (%) | St. Dev. (%) |
|---|---|---|---|---|
| 1 | Ig kappa chain C region | IGKC | 7.87 | 0.20 |
| 2 | Complement C3 | CO3 | 4.64 | 0.12 |
| 3 | Ig lambda-2 chain C regions | LAC2 | 3.65 | 0.09 |
| 4 | Complement C1q subcomponent subunit A | C1QA | 3.64 | 0.09 |
| 5 | Ig mu chain C region | IGHM | 2.93 | 0.07 |
| 6 | Complement C4-B | CO4B | 2.70 | 0.07 |
| 7 | Apolipoprotein C-III | APOC3 | 2.30 | 0.06 |
| 8 | Serum albumin | ALBU | 1.84 | 0.05 |
| 9 | Vitronectin | VTNC | 1.76 | 0.04 |
| 10 | Complement C1q subcomponent subunit B | C1QB | 1.75 | 0.04 |
| 11 | Apolipoprotein C-II | APOC2 | 1.66 | 0.04 |
| 12 | Keratin, type II cytoskeletal 1 | K2C1 | 1.59 | 0.04 |
| 13 | C4b-binding protein alpha chain | C4BPA | 1.57 | 0.04 |
| 14 | Hemoglobin subunit alpha | HBA | 1.54 | 0.04 |
| 15 | Ig gamma-1 chain C region | IGHG1 | 1.49 | 0.04 |
| 16 | Apolipoprotein A-II | APOA2 | 1.36 | 0.03 |
| 17 | Apolipoprotein E | APOE | 1.36 | 0.03 |
| 18 | Apolipoprotein A-I | APOA1 | 1.36 | 0.03 |
| 19 | Keratin, type I cytoskeletal 10 | K1C10 | 1.36 | 0.03 |
| 20 | Hemoglobin subunit beta | HBB | 1.35 | 0.03 |
| 21 | Keratin, type I cytoskeletal 9 | K1C9 | 1.23 | 0.03 |
| 22 | Complement C1q subcomponent subunit C | C1QC | 1.23 | 0.03 |
| 23 | Ig gamma-2 chain C region | IGHG2 | 1.20 | 0.03 |
| 24 | Thymosin beta-4 | TYB4 | 1.14 | 0.03 |
| 25 | Ig kappa chain V-III region HAH | KV312 | 1.12 | 0.03 |

**Table S19. List of descriptors used.** The list comprised n=14 corona proteins that are usually categorized as being positively correlated with NP cell association.

| | NP1 | NP2 | NP3 | NP4 | NP5 | NP6 | NP7 | NP8 | NP9 | NP10 | NP11 | NP12 | NP13 | NP14 | NP15 | NP16 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Apo AI** | 3.0 | 2.0 | 2.9 | 4.0 | 3.3 | 1.0 | 1.1 | 0.9 | 2.0 | 1.9 | 1.1 | 0.9 | 2.5 | 2.5 | 1.7 | 1.4 |
| **Apo AII** | 1.9 | 0.8 | 1.0 | 3.0 | 0.7 | 0.8 | 0.9 | 0.9 | 1.0 | 1.4 | 1.8 | 1.1 | 1.5 | 1.4 | 1.4 | 1.4 |
| **Apo B** | 1.2 | 0.4 | 0.8 | 1.6 | 0.7 | 0.6 | 0.6 | 0.8 | 1.3 | 1.0 | 0.7 | 0.6 | 0.8 | 1.0 | 0.8 | 0.6 |
| **Apo E** | 2.3 | 1.2 | 1.0 | 2.7 | 1.2 | 1.3 | 1.0 | 1.5 | 1.0 | 1.4 | 1.1 | 1.1 | 2.6 | 1.9 | 1.9 | 1.4 |
| **Apo CI** | 1.5 | 0.9 | 0.2 | 2.7 | 0.6 | 0.3 | 0.5 | 0.4 | 0.4 | 0.6 | 0.2 | 0.0 | 1.7 | 1.4 | 0.7 | 0.8 |
| **Apo CII** | 1.2 | 3.2 | 0.9 | 2.9 | 0.5 | 0.7 | 0.7 | 0.6 | 0.6 | 0.6 | 0.8 | 0.6 | 2.6 | 2.2 | 1.3 | 1.7 |
| **Fibrinogen** | 5.9 | 2.9 | 7.7 | 4.6 | 8.4 | 5.7 | 4.9 | 3.7 | 3.3 | 4.4 | 14.0 | 14.4 | 2.7 | 2.7 | 2.9 | 2.3 |
| **Integrin** | 0.8 | 0.5 | 0.1 | 1.2 | 0.2 | 0.1 | 0.1 | 0.1 | 0.1 | 0.3 | 0.4 | 0.2 | 0.4 | 1.2 | 0.6 | 0.7 |
| **Inter-alpha-trypsin** | 2.6 | 1.8 | 9.4 | 1.7 | 6.3 | 9.3 | 10.6 | 9.4 | 3.9 | 1.3 | 2.1 | 3.8 | 3.5 | 2.7 | 2.0 | 0.7 |
| **Keratin** | 6.4 | 1.3 | 2.5 | 9.1 | 2.6 | 2.2 | 2.6 | 1.9 | 3.5 | 5.6 | 14.3 | 14.2 | 6.0 | 8.4 | 7.0 | 7.3 |
| **Phrotrombin** | 0.8 | 1.1 | 4.1 | 0.7 | 3.0 | 7.7 | 8.3 | 7.6 | 1.6 | 0.4 | 0.8 | 0.2 | 1.5 | 0.8 | 0.5 | 0.2 |
| **Serotransferrin** | 1.2 | 0.5 | 0.6 | 1.0 | 0.6 | 0.4 | 0.4 | 0.6 | 0.8 | 1.0 | 0.5 | 0.4 | 0.5 | 0.5 | 0.6 | 0.5 |
| **Serum Albumin** | 4.2 | 8.6 | 4.7 | 5.6 | 4.6 | 1.9 | 2.2 | 2.7 | 5.6 | 7.3 | 5.8 | 3.0 | 1.3 | 1.3 | 2.5 | 1.8 |
| **Vitronectin** | 2.6 | 8.9 | 2.9 | 1.8 | 2.5 | 2.7 | 3.0 | 2.8 | 0.3 | 0.2 | 0.4 | 2.0 | 1.2 | 0.9 | 0.9 | 1.8 |

**Table S20.** Potential targets of protein corona fingerprints with its own interaction score (mentha) and the expression median value in Hela cells. *(Low Expression level < 8.5; 8.5 < Medium Expression level < 11.5; High Expression level > 11.5)

| Corona Protein | | Receptor Interactor (Interaction score of protein corona-receptor) | Hela * (GENEVESTIGATOR ) |
|---|---|---|---|
| **P04004\|VTNC_HUMAN** | **Vitronectin** | P18084 – ITGB5 (0.2098) | Median Value = 10.90<br>Conf. Int. (95%) = [10.77-11.13] |
| | | P06756 – ITGAV (0.2098) | Median Value = 15.53<br>Conf. Int. (95%) = [15.05-15.89] |
| **P02647\|APOA1_HUMAN** | **Apolipoprotein A-I** | O95477 – ABCA1 (0.523) | Median Value =9.14<br>Conf. Int. (95%) = [8.53-9.54] |
| | | O14798 – TNFRSF10C (0.2857) | Median Value =8.54<br>Conf. Int. (95%) = [8.36-8.68] |
| | | P29965 – CD40LG (0.2098) | Median Value =8.96<br>Conf. Int. (95%) = [8.89-9.13] |
| | | Q8WTV0 - SCARB1 (0.3939) | Median Value =14.47<br>Conf. Int. (95%) = [14.16-14.53] |
| **P02652\|APOA2_HUMAN** | **Apolipoprotein A-II** | P13569– CFTR (0.12959) | Median Value =9.02<br>Conf. Int. (95%) = [8.74-9.28] |
| | | Q8WTVO - SCARB1 (0.393) | Median Value =14.47<br>Conf. Int. (95%) = [14.16-14.53] |
| **P04114\|APOB_HUMAN** | **Apolipoprotein B-100** | P01130 – LDLR (0.6706) | Median Value =14.16<br>Conf. Int. (95%) = [13.71-14.98] |
| | | P00533 – EGFR (0,1259) | Median Value =13.42<br>Conf. Int. (95%) = [13.15-13.73] |
| | | P30988 – CALCR (0,4543) | Median Value =8.13<br>Conf. Int. (95%) = [8.0-8.34] |

**Effect of exposure to human plasma on size and zeta potential of NPs**

The simplest theoretical model of NP agglomeration is based on collisions between rigid spheres experiencing Brownian diffusion. Coagulation is controlled by Van der Waals interactions and can be described by collision rates. Although, in general, the clustering process defines a nonlinear dynamical system, it can be regarded as a sphere-packing problem (R. M'Hallah, A. Alkandari, and N. Mladenovic, Computers & Operations Research 40, 2013, 603). DLS experiments provide hydrodynamic diameter of NPs, i.e. $D_H$. According to the dense spherical packing model, the smallest sphere containing two equal rigid spheres of radius R has radius 2R. Following 1-hour incubation with human plasma, the hydrodynamic diameter of 13 nanoparticle-protein complexes, $D_H$, was found to be definitely smaller than double the diameter of pristine nanoparticles, $D_{H0}$ (Figure S1, panel A, black circles). This indicates that incubation did not produced appreciable particle aggregation. For 3 formulations (NP1, NP2 and NP7) $D_H/ D_{H0} \approx 2$ is compatible with formation of dimers. Change in size ($D_H$-$D_{H0}$) as a function of both $D_{H0}$ and $D_H$ is reported in panels B and D respectively. Changes in zeta-potential ($ZP$-$ZP_0$) after plasma exposure is plotted against both $ZP_0$ and $ZP$ in panels C and E respectively.

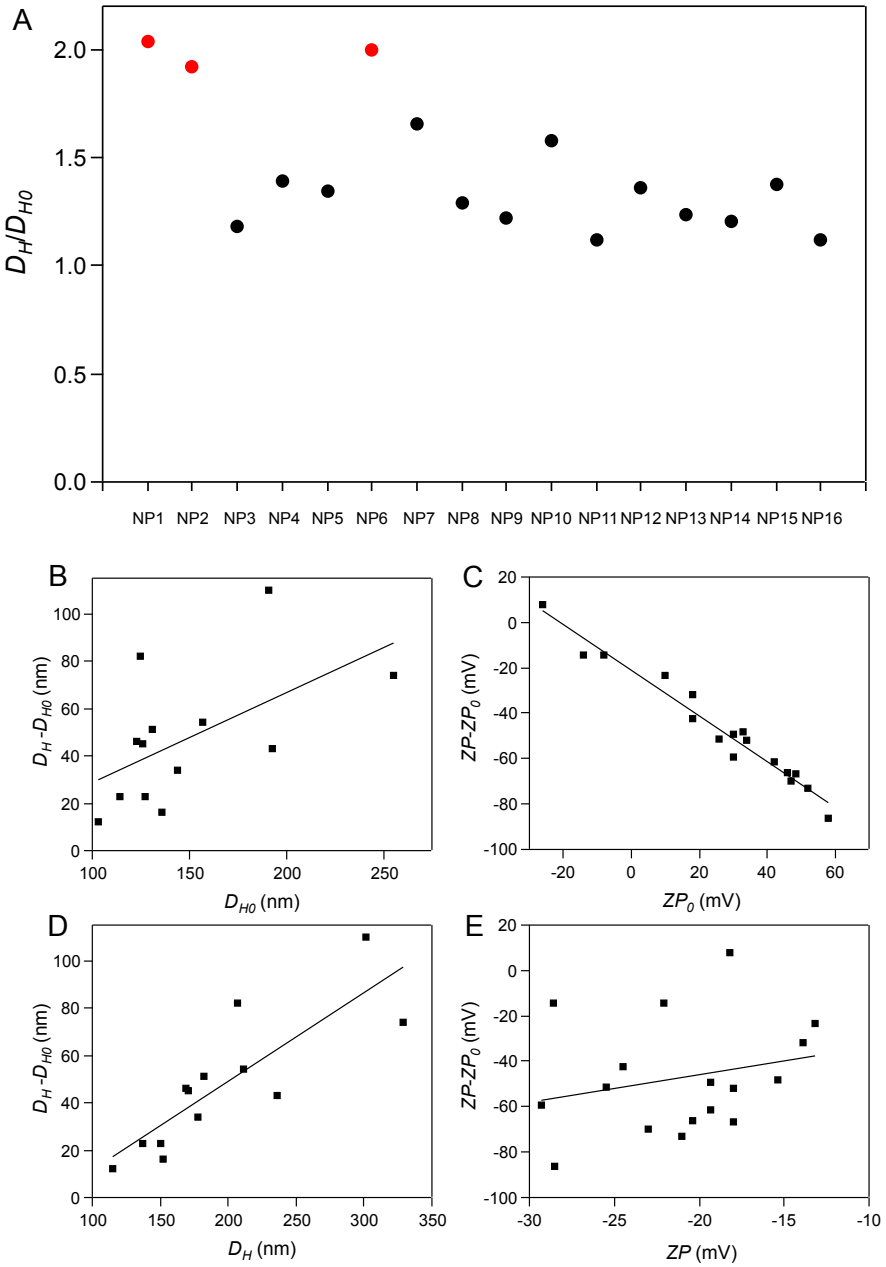


**Figure S1.** (A) Ratio between the average hydrodynamic diameters of NPs after ($D_H$) and before ($D_{H0}$) incubation with human plasma, $D_H/D_{H0}$. For 13 nanoparticle-protein complexes (black circles) $D_H/D_{H0}$ is definitely < 2 indicating that incubation did not produced appreciable particle aggregation. 3 nanoparticle formulations exhibited an increase in size that is compatible with formation of dimers (red circles). (B) Increase in size ($D_H$-$D_{H0}$) as a function of the size of NPs after synthesis, $D_{H0}$. (C) Change in zeta-potential ($ZP$-$ZP_0$) after plasma exposure as a linear function of the zeta-potential after synthesis. (D) Increase in size ($D_H$-$D_{H0}$) of the 13 monodisperse HC-coated as linear function of $D_H$. (E) Change in zeta-potential ($ZP$-$ZP_0$) after plasma exposure as a function of the zeta-potential after incubation with human plasma. Solid lines are the best linear fits to the data ($R^2$=0.318; 0.960; 0.691; 0.061 for linear plots of panels B, C, D and E respectively). The High prediction accuracy ($R^2$=0.960) indicates that the change in zeta-potential ($ZP$-$ZP_0$) of NPs after plasma exposure is a linear function of the zeta-potential after synthesis (C).

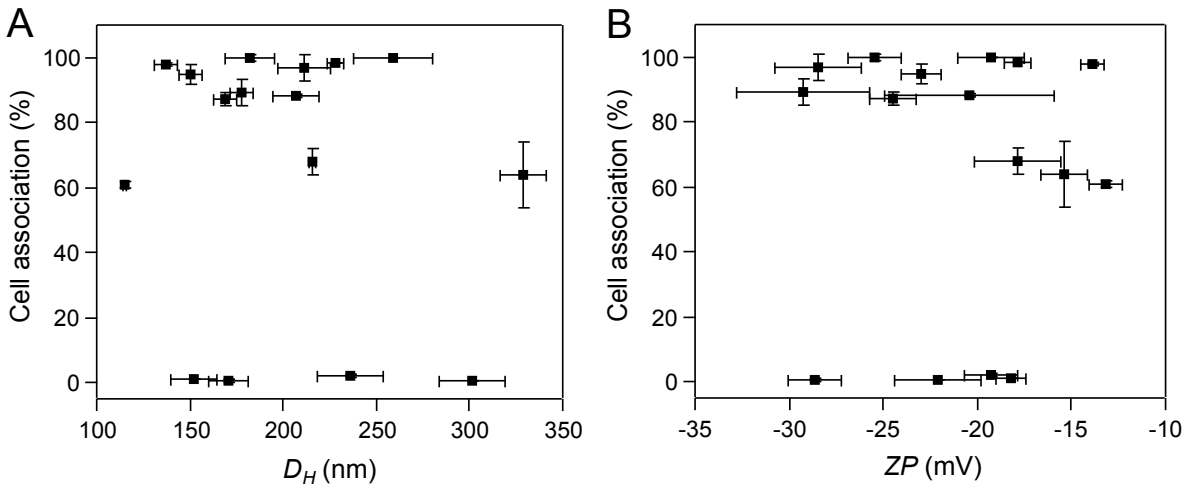


**Figure S2.** (A) NP-cell association plotted as a function of size of HC-coated NPs. (B) NP-cell association plotted as a function of zeta-potential of HC-coated NPs. As evident, no clear trend was found. This finding demonstrates that none of the NPs' physicochemical properties alone (size, zeta-potential and aggregation state) is able to account for association with HeLa cells (Considerations about aggregation state are given in Figure S1, panel A).

**Predictive modeling of nanoparticle-cell association**

To determine which protein fingerprints promote cell association, we adopted an iterative two-step approach, based on the prediction accuracy of an exponential-like saturation model. The aim is to define a subset Γ* of all (N=436) the detected relative protein abundances (RPAs), such that the reference functional relationship

$$f(x) = 100[1 - exp\{-b(x - x_0)\}] \quad (1)$$

fits the cell association with the highest fitting determination coefficient $R^2$. The sum of the RPAs belonging to a subset Γ represents the independent variable in Eq. 1. The first step of the procedure explores all the partial sums, which can be defined from a starting set of n≤N elements. Thus, for any k-values (k≤n), n!/k!(n-k)! fitting curves are obtained, each for any possible sum of k terms belonging to a set of n elements. Since the number of possible partial sums rapidly increases with n, is not possible to include all the detected RPAs in this step of the computation. Thus, we chose n=14 proteins as starting set of descriptors. The list comprised corona proteins that are usually categorized as being positively correlated with NP cell association. The dependence of the cell association on each partial sum has been evaluated by least square method and the highest $R^2$-value, namely $R_0^2$, defines a starting subset $\Gamma_0$ of $k_0$ protein corona fingerprints (Figure S3, panel A, red circles).

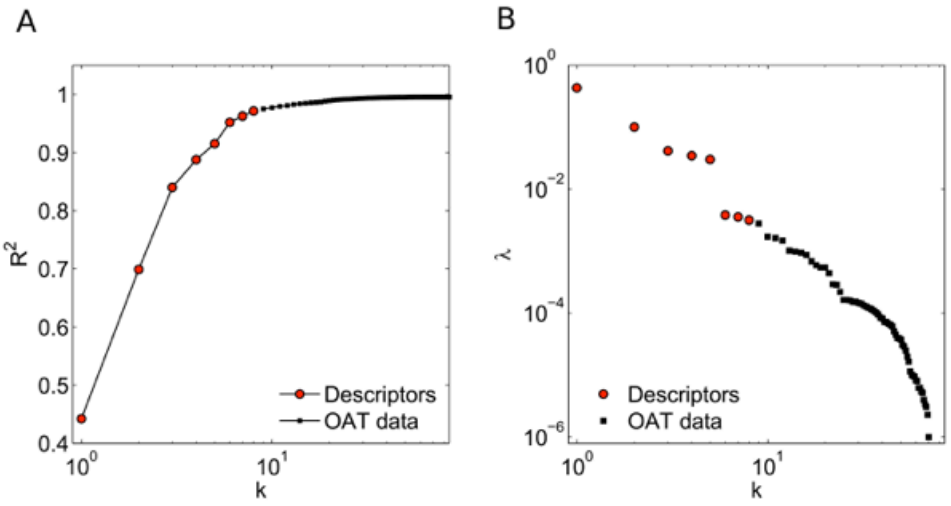


**Figure S3.** (A) Accuracy of predictive modeling of nanoparticle cell association and (B) ranking coefficient of proteins, λ, in their ability to promote nanoparticle-cell association.

In order to extend the analysis over the N-n excluded proteins, we adopted the following one-at-a time (OAT/OFAT) method as a second step of computation. Then, we iterated the whole procedure until a convergence criterion was fulfilled. In detail, n-$k_0$ subsets have been obtained by adding the single RPAs not belonging to $\Gamma_0$, one at a time. We fitted the cell association through f and evaluated the corresponding $R^2$-values. The maximum $R^2$-value determines a subset of $k=k_0+1$ elements, which can be used as a new starting point for a further one-at-a-time computation. By iterating the procedure, all the proteins are included in the analysis. On the other hand, the first added protein $p_1$ could be more relevant to the fitting curve than some elements belonging to the starting subset $\Gamma_0$. In order to investigate this situation, $p_1$ has been included in the initial set of descriptors and the step I has been iterated, with the subsequent definition of a new subset $\Gamma_1$. If an improvement of the prediction accuracy results for $k<k_0+1$, then $p_1$ is promoted to descriptor and a new one-at-a-time step is carried out by using $\Gamma_1$ as starting set. Otherwise, the procedure can be stopped. This defines the convergence criterion of the adopted method. When the convergence is fulfilled, a definitive curve of $R^2$ as a function of k is obtained (Figure S3, panel A). $R^2$ increases with k until it reaches a maximum, then it is stable at a plateau value and finally decreases toward zero (not shown). The first $k^*=8$ data points correspond to the final pool of descriptors, the other ones represent less relevant further contributions. Indeed, these are responsible for relative increases of the prediction accuracy lower than 1%. Furthermore, a protein ranking can be defined. More precisely, the final step of the aforementioned method determines a maximum measured $R^2$-value, namely $R_M^2=0.9954$. Thus, if the RPA of the i-th protein is excluded to the computation, the corresponding prediction accuracy decreases to $R_i^2<R_M^2$ and subsequently, a specific contribution $\lambda_i$ can be uniquely determined as follows:

$$\lambda_i = \frac{R^2{}_M - R^2{}_i}{R^2{}_M} \quad (2)$$

As a result, proteins are ranked in terms of their ability to promote cell association (Figure S3, panel B).