This arena is already EU-US

J|A|C|S ARTICLES

What the Cell "Sees" in Bionanoscience

Dorota Walczyk,[†,‡] Francesca Baldelli Bombelli,[*,†,‡] Marco P. Monopoli,[†,‡] Iseult Lynch,[†,‡] and Kenneth A. Dawson[*,†,‡]

nature nanotechnology LETTERS
PUBLISHED ONLINE: 19 DECEMBER 2010 | DOI: 10.1038/NNANO.2010.250

Nanoparticle-induced unfolding of fibrinogen promotes Mac-1 receptor activation and inflammation

Australia!

Zhou J. Deng[1], Mingtao Liang[2,3], Michael Monteiro[4], Istvan Toth[2,3] and Rodney F. Minchin[1]*

nature materials REVIEW ARTICLE
PUBLISHED ONLINE: 14 JUNE 2009 | DOI: 10.1038/NMAT2442

Understanding biophysicochemical interactions at the nano–bio interface

Andre E. Nel[1]*, Lutz Mädler[2], Darrell Velegol[3], Tian Xia[1], Eric M. V. Hoek[4], Ponisseril Somasundaran[5], Fred Klaessig[6], Vince Castranova[7] and Mike Thompson[8]

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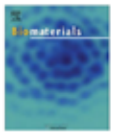

The influence of protein adsorption on nanoparticle association with cultured endothelial cells

Morton S. Ehrenberg[a,*], Alan E. Friedman[b], Jacob N. Finkelstein[b], Günter Oberdörster[b], James L. McGrath[a]

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[b] Department of Environmental Medicine, University of Rochester, Rochester, NY, United States

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Nanomedicine: Nanotechnology, Biology, and Medicine 5 (2009) 106–117
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Gold Nanoparticles: Feature Article

Interaction of colloidal gold nanoparticles with human blood: effects on particle size and analysis of plasma protein binding profiles

Marina A. Dobrovolskaia, PhD,* Anil K. Patri, PhD, Jiwen Zheng, PhD, Jeffrey D. Clogston, PhD, Nader Ayub,[1] Parag Aggarwal, PhD, Barry W. Neun, BS, Jennifer B. Hall, PhD, Scott E. McNeil, PhD

J|A|C|S ARTICLES
Published on Web 03/07/2006

Surface Tailoring for Controlled Protein Adsorption: Effect of Topography at the Nanometer Scale and Chemistry

Paul Roach,[†] David Farrar,[‡] and Carole C. Perry*[,†]

nature nanotechnology LETTERS
PUBLISHED ONLINE: 15 AUGUST 2010 | DOI: 10.1038/NNANO.2010.164

An index for characterization of nanomaterials in biological systems

Xin-Rui Xia, Nancy A. Monteiro-Riviere and Jim E. Riviere*

Correlating Physico-Chemical with Toxicological Properties of Nanoparticles: The Present and the Future

Pilar Rivera Gil,[†] Günter Oberdörster,* Alison Elder,* Victor Puntes,[§] and Wolfgang J. Parak*[,†]

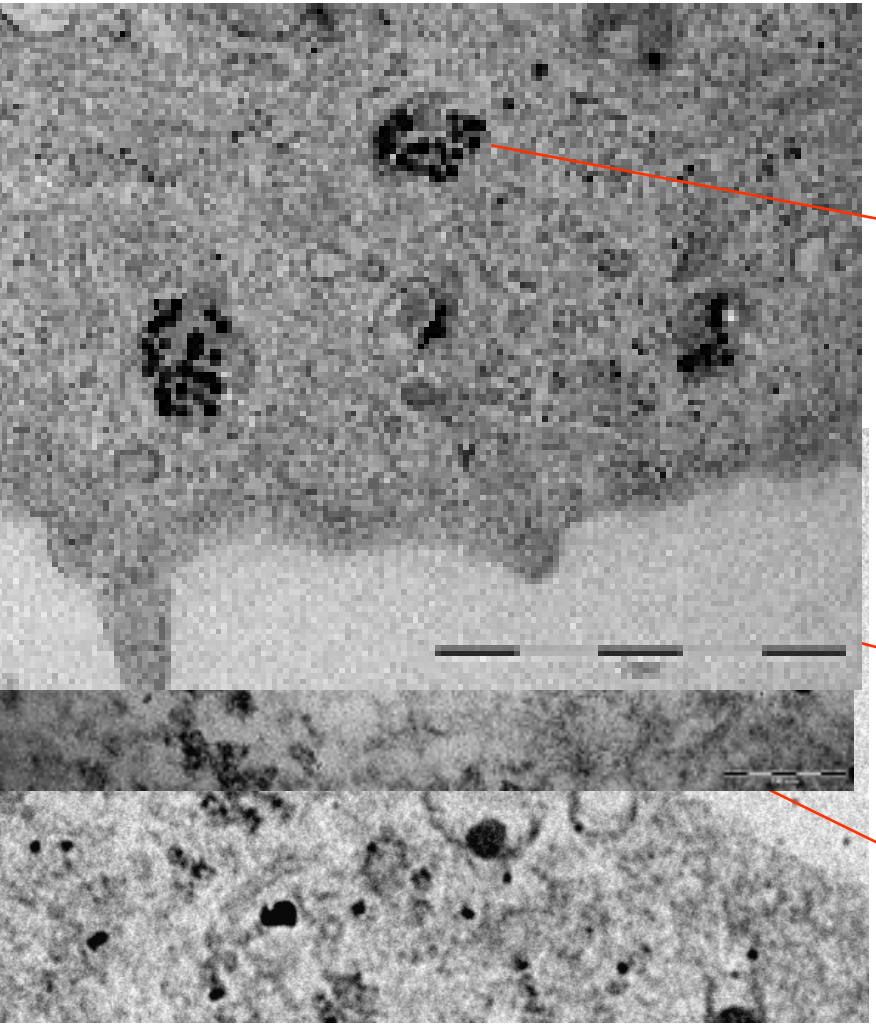
[†]Fachbereich Physik and WZMW, Philipps Universität Marburg, Marburg, Germany, [‡]Department of Environmental Medicine, University of Rochester, Rochester, New York, and [§]Institut Català de Nanotecnologia, Campus UAB Barcelona, Spain

LETTERS
nature biotechnology

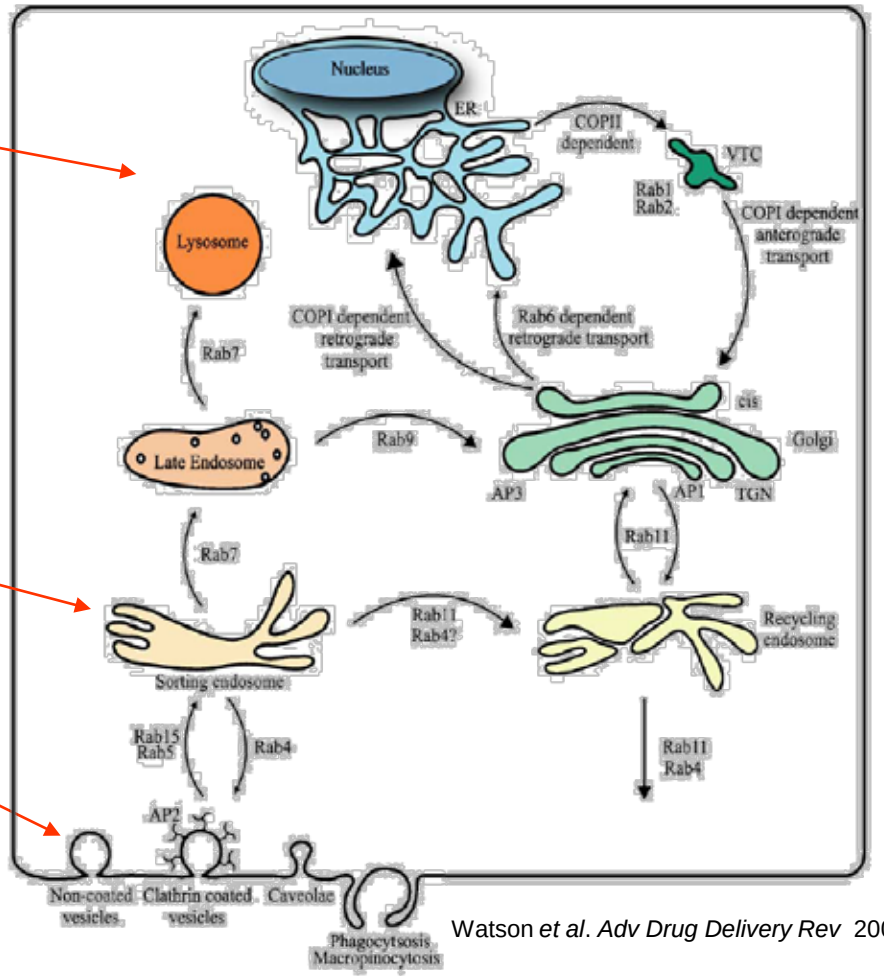
Rapid translocation of nanoparticles from the lung airspaces to the body

Nanoparticles travel into cell via Existing energy dependent pathways

Recognition Motifs and 'Identity' Matters

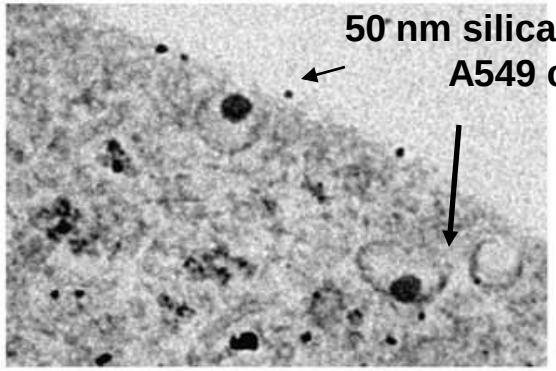


Salvati, A Time and space resolved uptake study of silica nanoparticles by human cells. Mol Biosyst, 7, 371-378



Watson *et al*. *Adv Drug Delivery Rev* 2005

Interactions with Living World Occur Via Interface

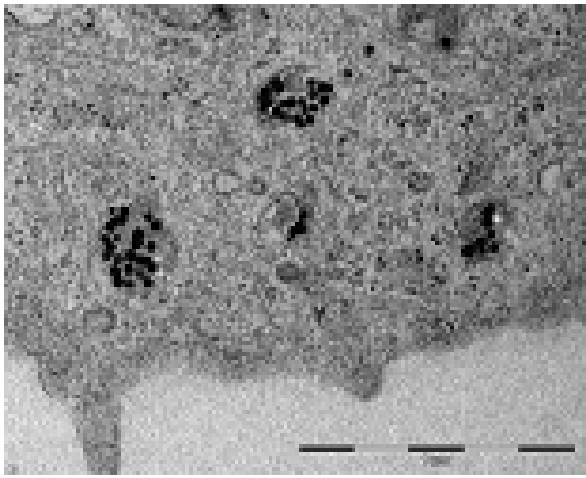


Cedervall, T.Understanding the nanoparticle-protein corona

Proc Natl Acad Sci U S A 2007, *104*, 2050-2055.

Size, shape, other Factors matter

Surface (interface) Main element of 'Biological' identity

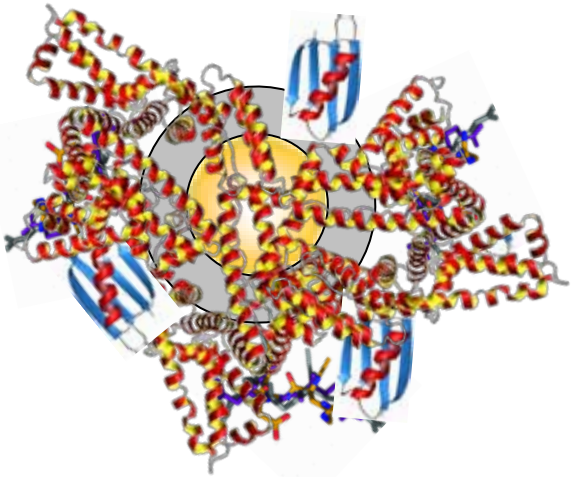


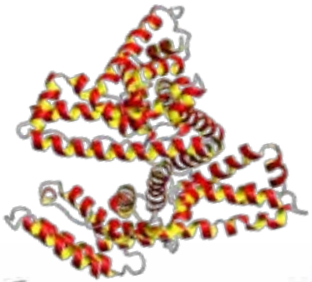
This cell has 2 square microns Of interface; in lysosomes-for ever

Hypothesis of Biological Identity

Defined by exchange at the In situ Interface

Cozzarelli Prize NAS 2008

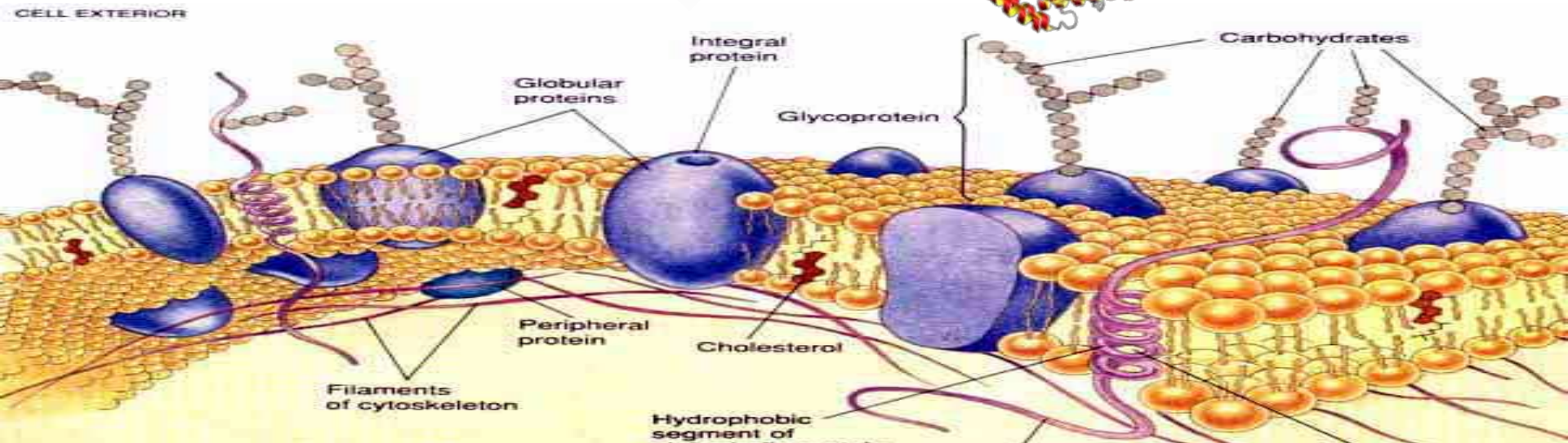




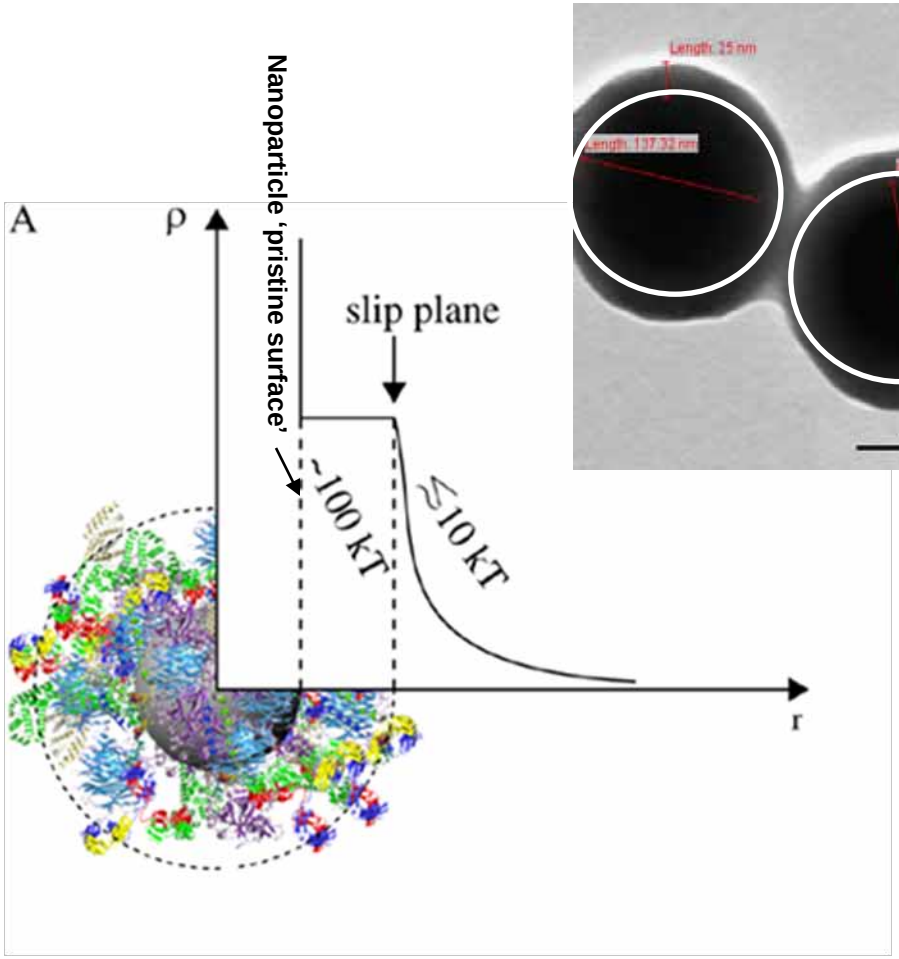
PNAS, 2007, 104, 2050-2055

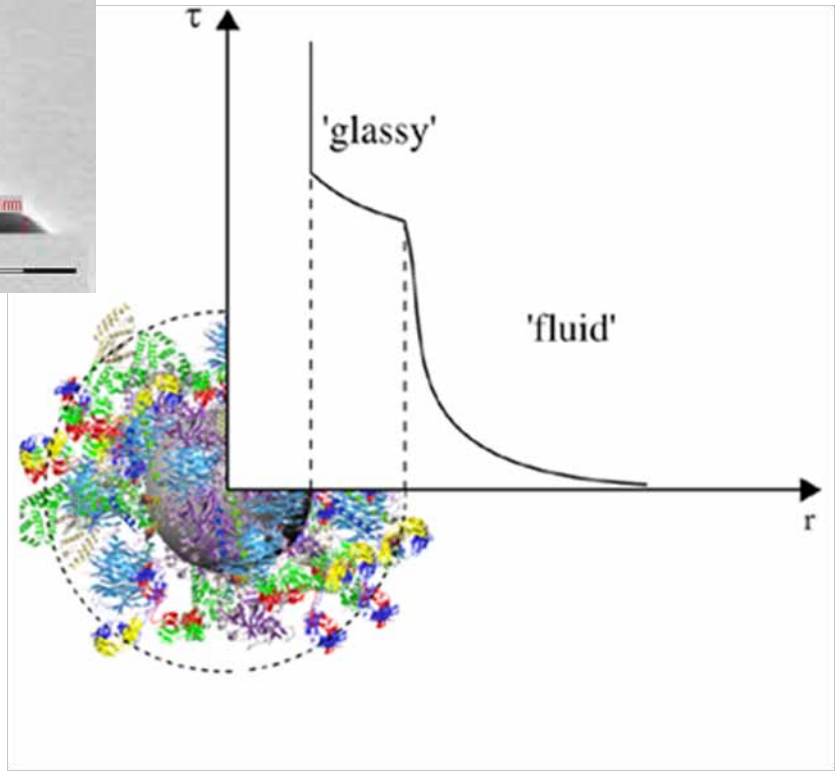
NATURE NANO, 2009, 4, 546

JACS, 2010, 2011



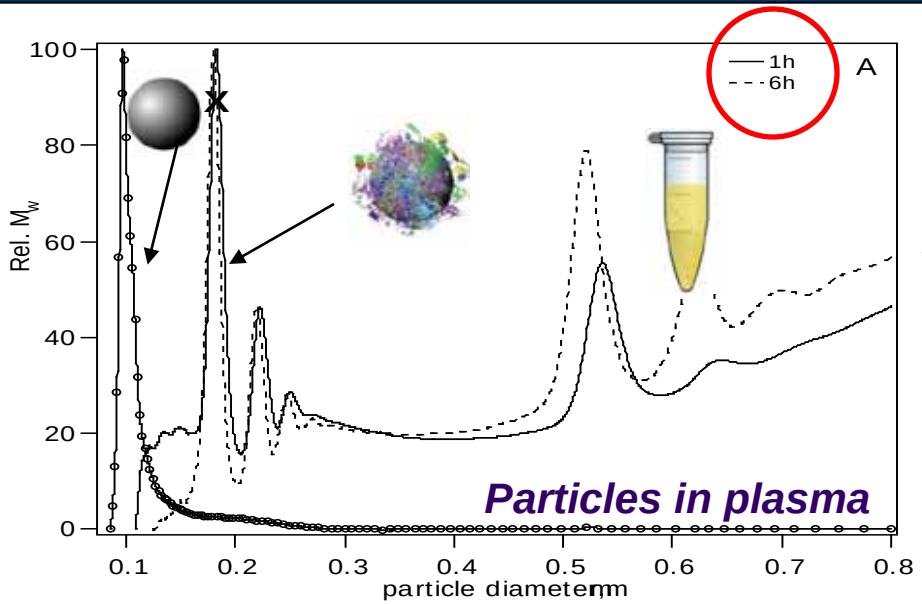
Typical Engineered Nanoparticle Physiochemical Nature of the *Interface with Living World*

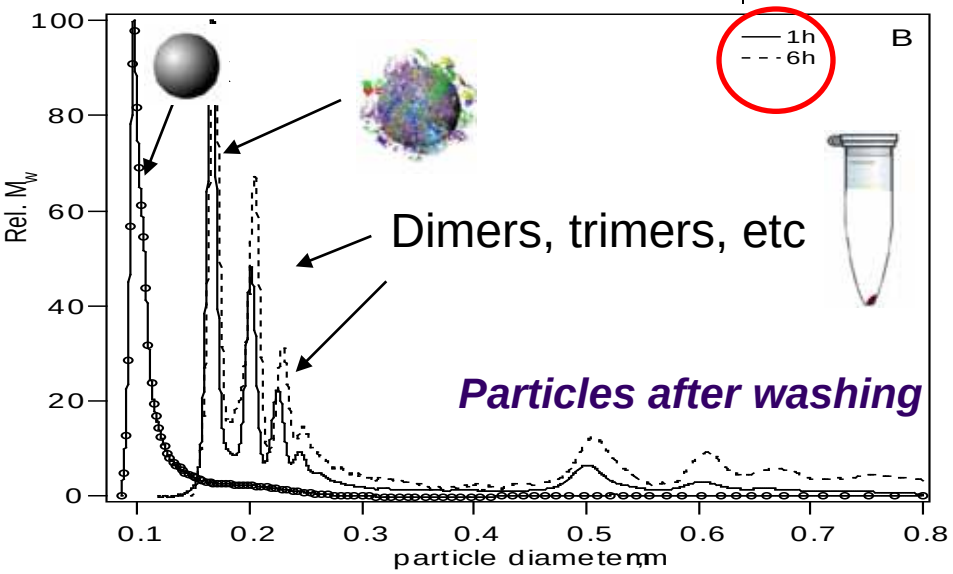


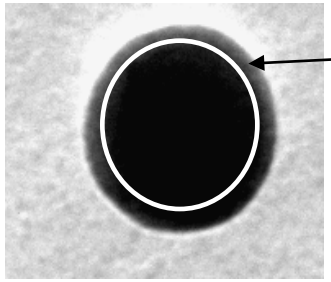


Walczyk, D What the cell "sees" in bionanoscience. *J Am Chem Soc*,(2010) *132*, 5761-5768

‘Hard Corona’ Nanoparticles are surface covered by proteins







Lighter shell is a rudimentary visualization of the corona

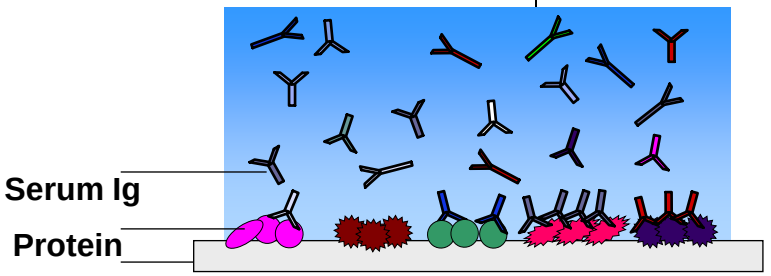
Protein coatings persist in time, and do change

Washing the particles does not remove the corona

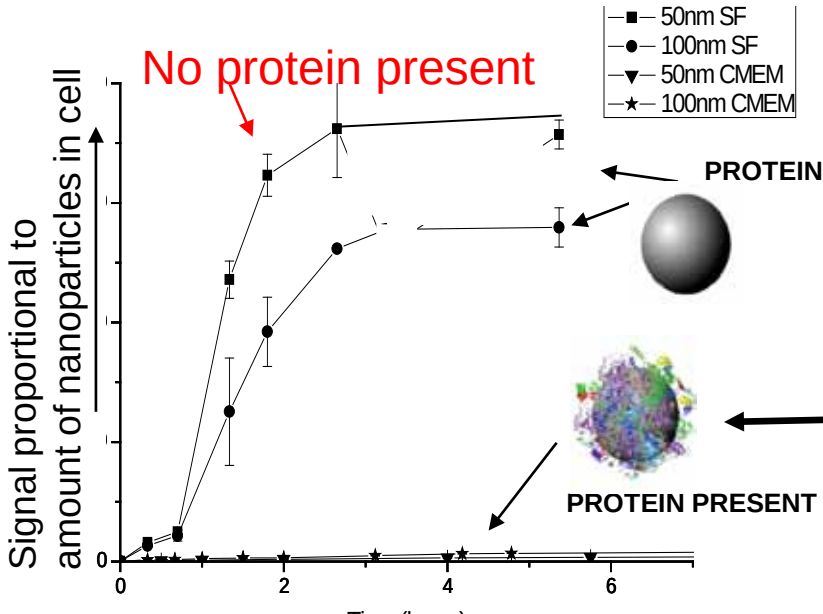
Walczyk, D. *J Am Chem Soc*,(2010) *132*, 5761-5768; Pitek *et al.* JACS 2011

Interactions of Nanoparticle with Cells, others surfaces, and extracellular matrix Determined by Hard Corona

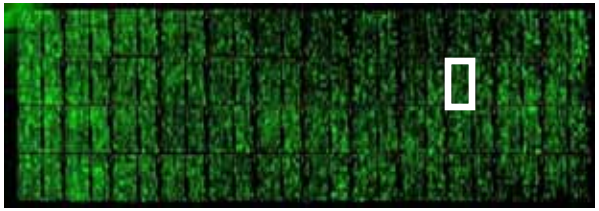
Protein Array (>10,000 proteins)
Used to assess interactions of nano
Particle-corona with 'all' human proteins

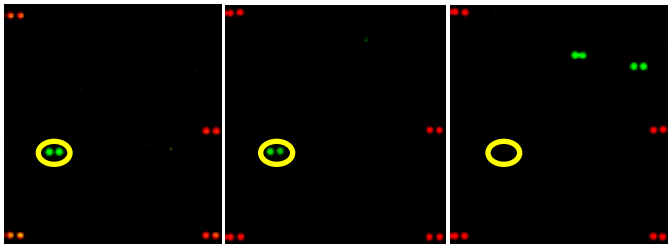


Pristine Surface of Nanoparticle Interacts with 'everything'
Particle in Presence of Biological (and Environmental) more specific



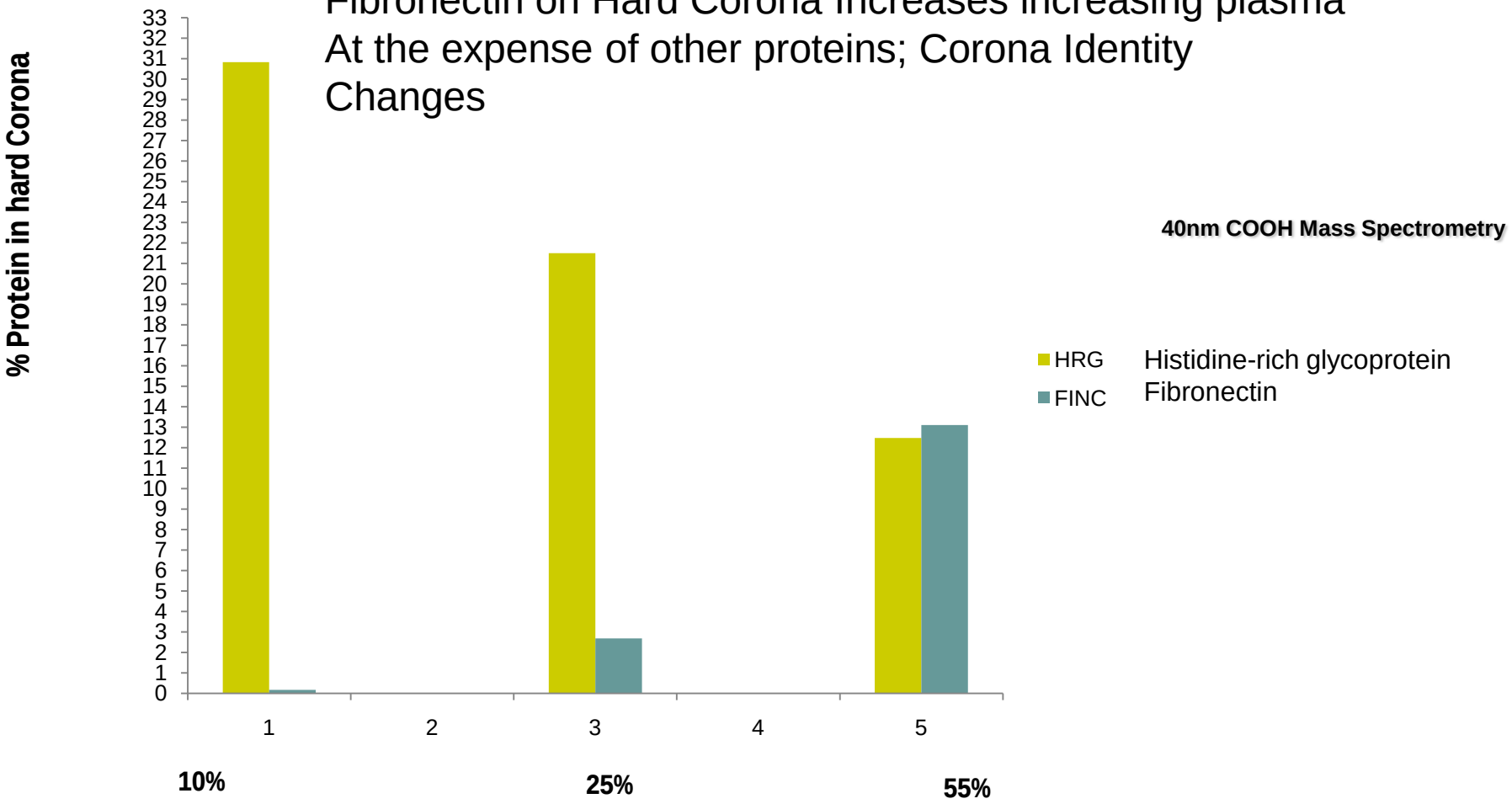
Non-Specific Interactions of Nanoparticles ubiquitous



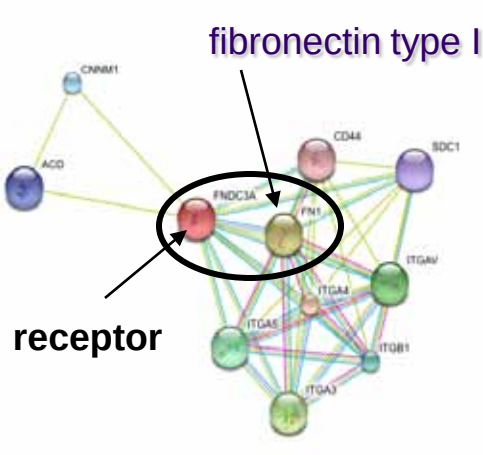


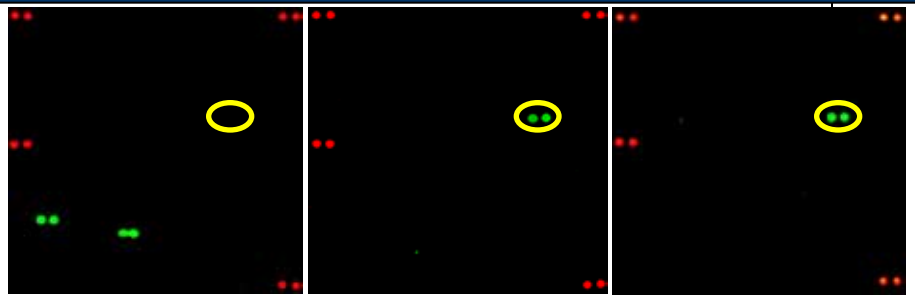
Changing hard corona with Increasing % Plasma
Competitive Biomolecule Exchange Changes Identity

Fibronectin on Hard Corona Increases increasing plasma
At the expense of other proteins; Corona Identity Changes



Human Plasma at inreasing concentration Receptor For Fibronectin Targetted *In Vivo* conditions FNDCA3 Signal Intensity

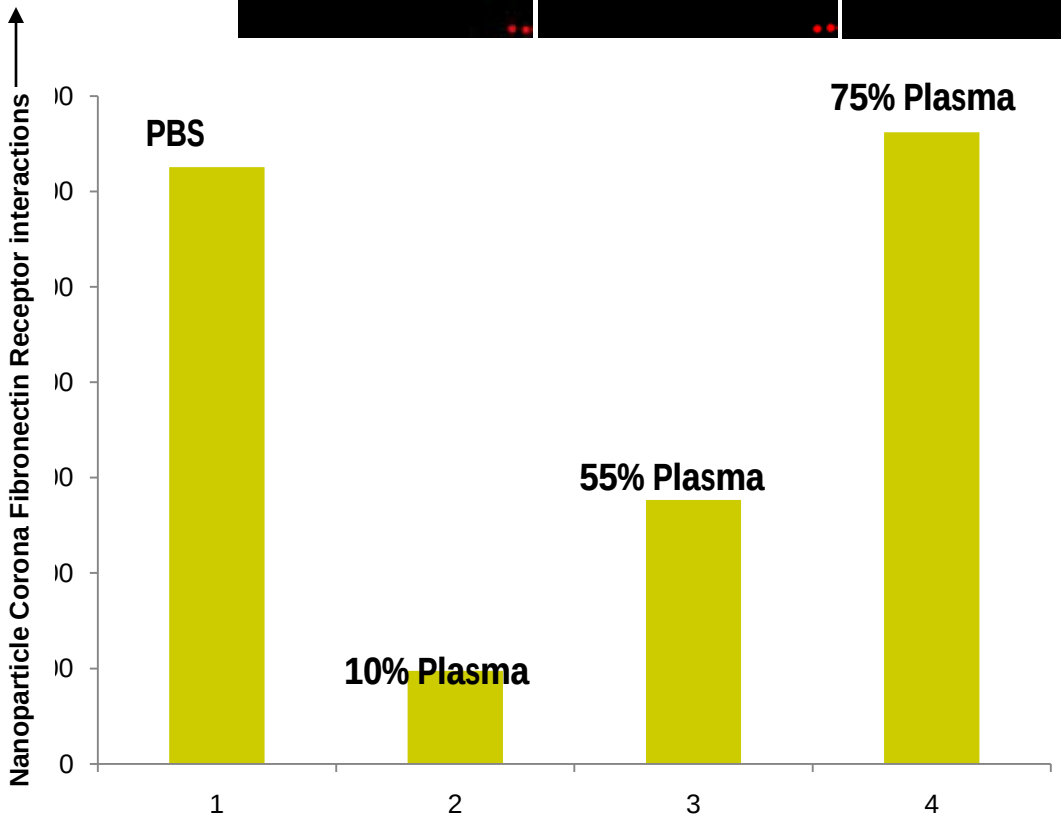




Without Protein Huge Non-Specific nanoparticle Surface-surface Interactions

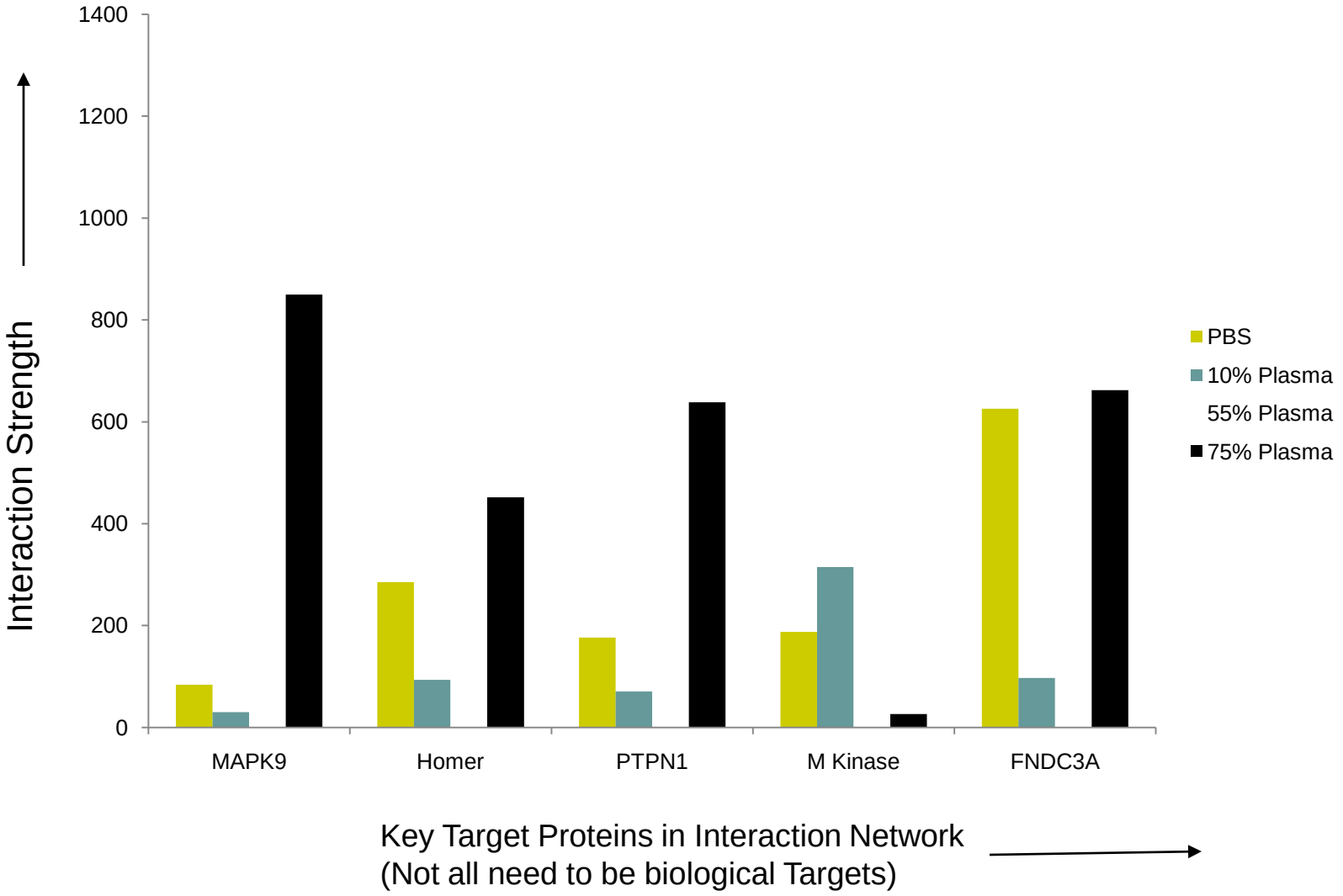
'In between-here 10%-Interactions 'cancel'

In presence of High Protein, Specific interactions



The Nanoparticle-Corona Biomolecular Complex Interactome

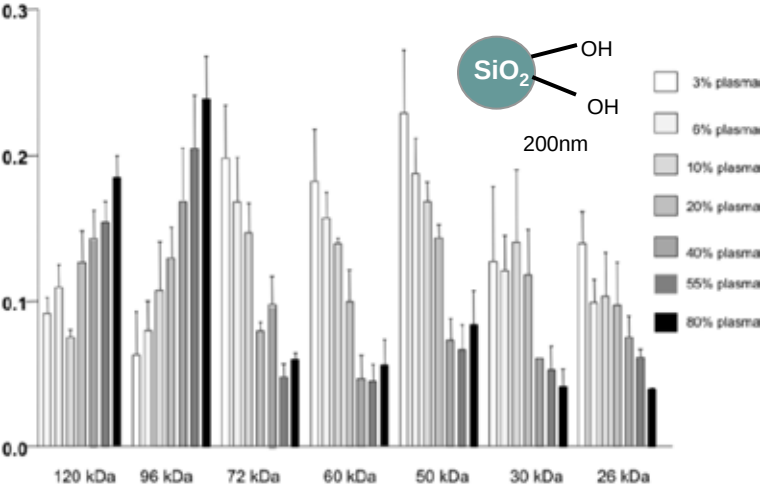
Increasing Plasma Concentration

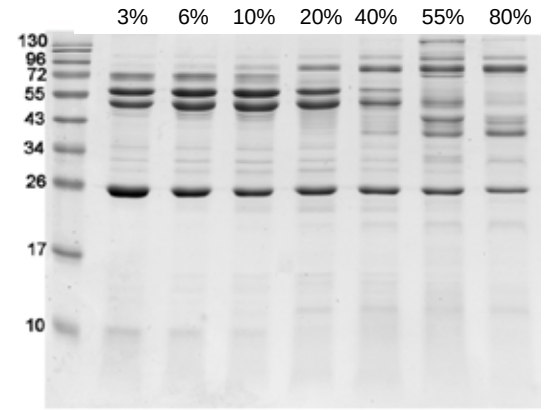


Hard corona Changes With different Biological (environmental) Fluid

Identity is Context Dependent

Densitometry of SDS-Page Gel





NPs incubated with different plasma concentrations to mimic *in vitro* and *in vivo* conditions

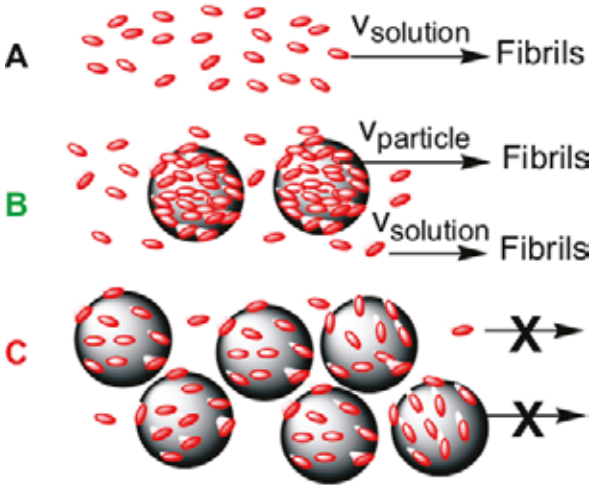
Here Biological Indentity Changes going From experimental in cell to in vivo conditions

Gel band Mw	Acc number	Protein Identity Spectral Counts	NSpC [10% plasma]	NSpC [55% plasma]
500kDa	P04114	Apolipoprotein B 100	0.96	0.91
120kDa	P07996	Thrombospondin-1	0.01	1.37
90 kDa	P04196	Histidine-rich glycoprotein	4.02	13.93
90 kDa	P00747	Plasminogen	0.87	3.27
90 kDa	P02787	Transferrin	0.02	0.52
72 kDa	P06396	Gelsolin	-	0.63
90 kDa	P02671	Fibrinogen alpha chain	15.43	4.88
72 kDa	P02768	Serum albumin	1.80	9.67
72 kDa	P01042	Kininogen-1	1.54	2.22
60 kDa	P02675	Fibrinogen beta chain	23.92	7.99
50 kDa	P02679	Fibrinogen gamma chain	18.40	6.52
50 kDa	P00748	Coagulation factor XII	1.05	4.15
43 kDa	P49908	Selenoprotein P	0.16	0.87
40 kDa	P02765	Alpha-2-HS-glycoprotein	-	0.16
28 kDa	P02749	Beta-2-glycoprotein	-	0.74
30 kDa	P02649	Apolipoprotein E	3.13	3.87
30 kDa	P02746	Complement C1q subcomponent Beta	2.28	0.58
26 kDa	P02647	Apolipoprotein A-I	9.45	14.83
12 kDa	P01834	Ig kappa chain C region	3.26	5.13

Monopoli, M..Relevance to in Vitro and in Vivo Biological Impacts of Nanoparticles. J Am Chem Soc. February 2, 2011

Protein unfolding, Protein Fibrillation
unexpected epitopes
Targets unexpected Receptors

Nucleation and growth of protein fibrils.



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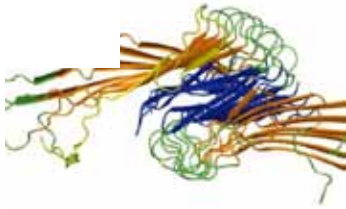
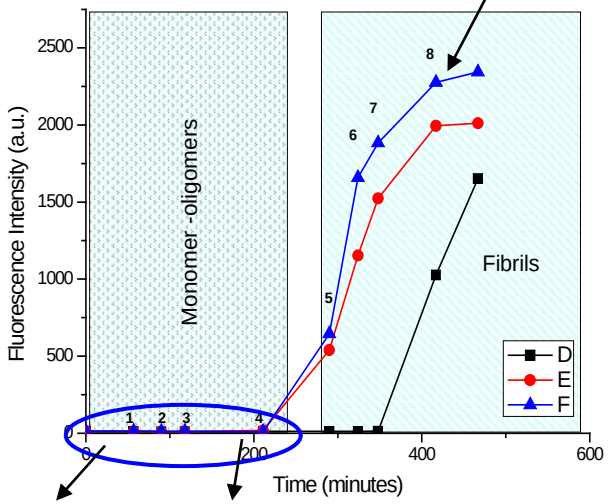


Exponential
Growth (elongation)

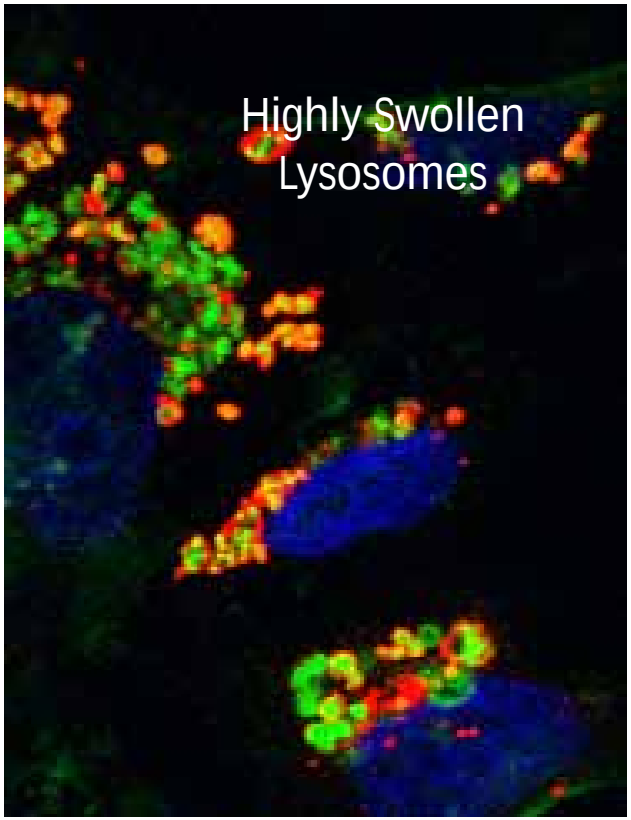


Particle protein disruption-unfolding at the surface

Cabaleiro-Lago C., *Proc. Natl. Acad. Sci. USA*, **104** (21); 8691-8696 (2007)

Two More Examples
Trojan Horse effect of corona
Corona determines biodistributions?

'positive' Particles apoptosis
Corona screens positive charge
Which is re-expressed at destination



A. Salvati and B. Wong

Protein corona determines
Destination of nanoparticles
In vivo

LETTERS

nature biotechnology

Rapid translocation of nanoparticles from the lung airspaces to the body

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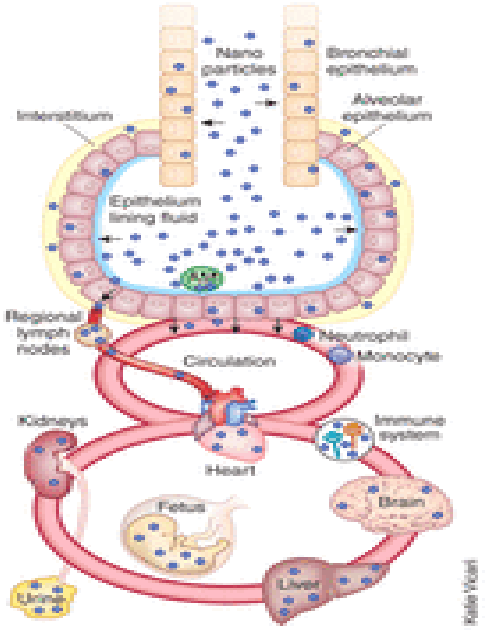

W. Kreyling picture

Watson 2005

Messages

- ACUTE HAZARDS IN WHOLE FIELD LESS THAN EXPECTED

- 'REAL' IN SITU IDENTITY OF NANOPARTICLE-fundamental for

  - Hazard classification
  - Biokinetics,Biodistributions
  - Parameters for ADME and QSARS
  - Might not be as complex as we think?!

- SURFACE ADSORBED SPECIES (ENVIRONMENT AND LIFE CYCLE ISSUE)

- FRAME RESEARCH TO EVALUATE HYPOTHESES (CHARACTERISE RIGHT THINGS ETC)

- IF 'INTEFACE' IS (OFTEN) WHAT MATTERS, NEED NEW 'TOOLS'

BY UNDERSTANDING THESE ISSUES WE HAVE THE POTENTIAL TO MAKE INNOVATION SAFE FOR A GENERATION