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Some publications

UCD DUBLIN

Lynch I, Salvati A and Dawson KA. Protein-nanoparticle interactions: What does the cell see? Nature Nanotechnol. 4, 546-547 (2009).

Cedervall T, Lynch I, Lindman S, Berggård T, Thulin E, Nilsson, H, Linse S, Dawson KA. Understanding the nanoparticle protein corona using methods to quantify exchange rates and affinities of proteins for nanoparticles, *PNAS*, 104, 2050-2055 (2007).

Walczyk D, Baldelli-Bombelli F, Campbell A, Lynch I and Dawson KA. What the Cell "Sees" in Bionanoscience, *J. Am. Chem. Soc.*, **2010**, *132* (16), pp 5761–5768 (2010)

Salvati A, dos Santos T, Varela J, Åberg C, Pinto P, Lynch I and Dawson KA. Experimental and theoretical approach to comparative nanoparticle and small molecule intracellular import, trafficking, and export. In press, Molecular Biosystems (2010)

Lundqvist M, Stigler J, Cedervall T, Elia G, Lynch I, and Dawson KA. Nanoparticle Size and Surface Properties determine the Protein Corona with possible implications for Biological Impacts. *PNAS*, 105, 14265-14270 (2008).

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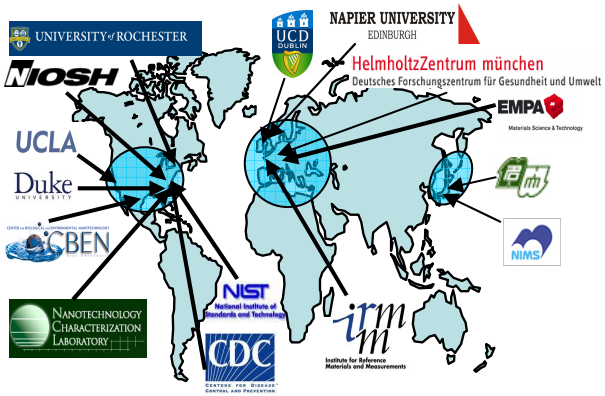
PEOPLE COMMUNITY RESOURCES

Students from 14 countries
majority funds EU internationally
26 companies from around the world



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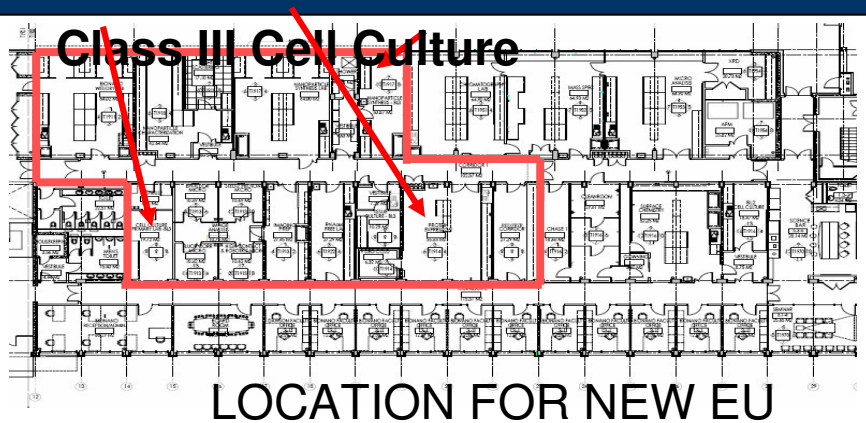

LOCATION FOR NEW EU INFRASTRUCTURE FOR BIONANOINTERACTIONS AND NANOSAFETY

Cozzarelli Prize, 2008

SFI SRC, EPA, HEA

http://www.cbni.eu

Centre for BioNano Interactions

FP RESEARCH

NANOINTERACT

NanoImpactNet

NeuroNano

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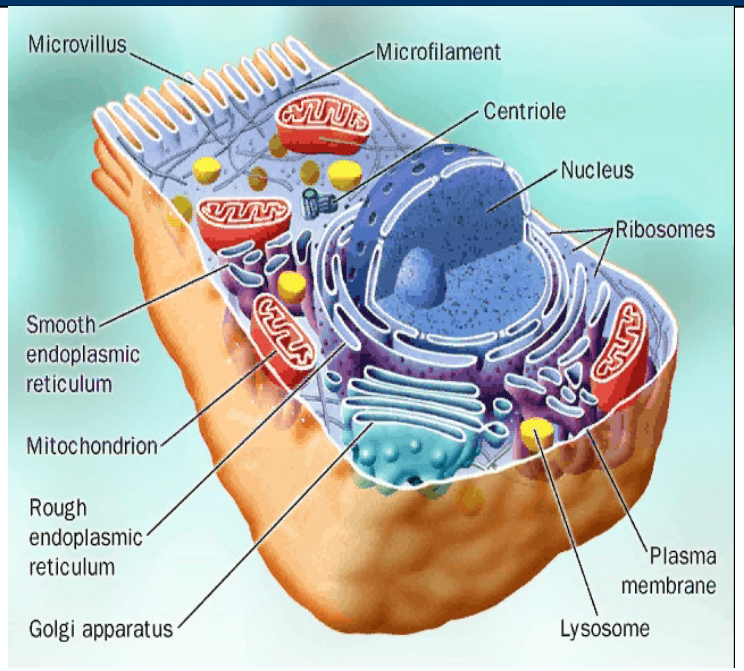
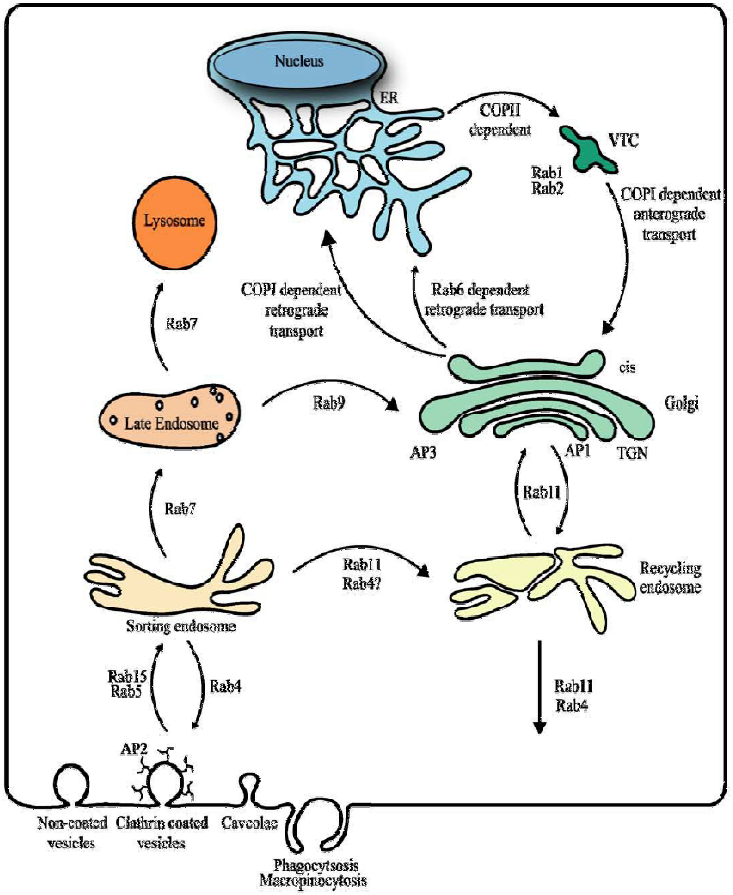
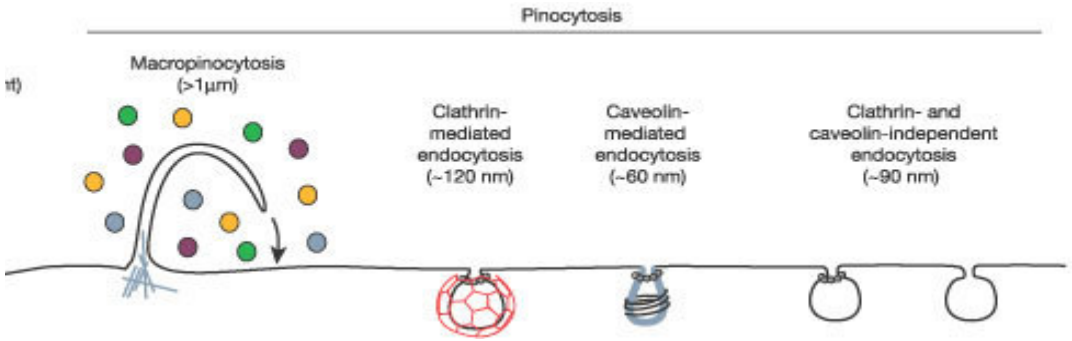
The Durable Issues
Nanoparticles in contact with living matter







CHEMICALS PARTITION …….NANOPARTICLES PROCESSED!

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Typical quantitative Uptake Nanoparticles Non-Specialized Cells

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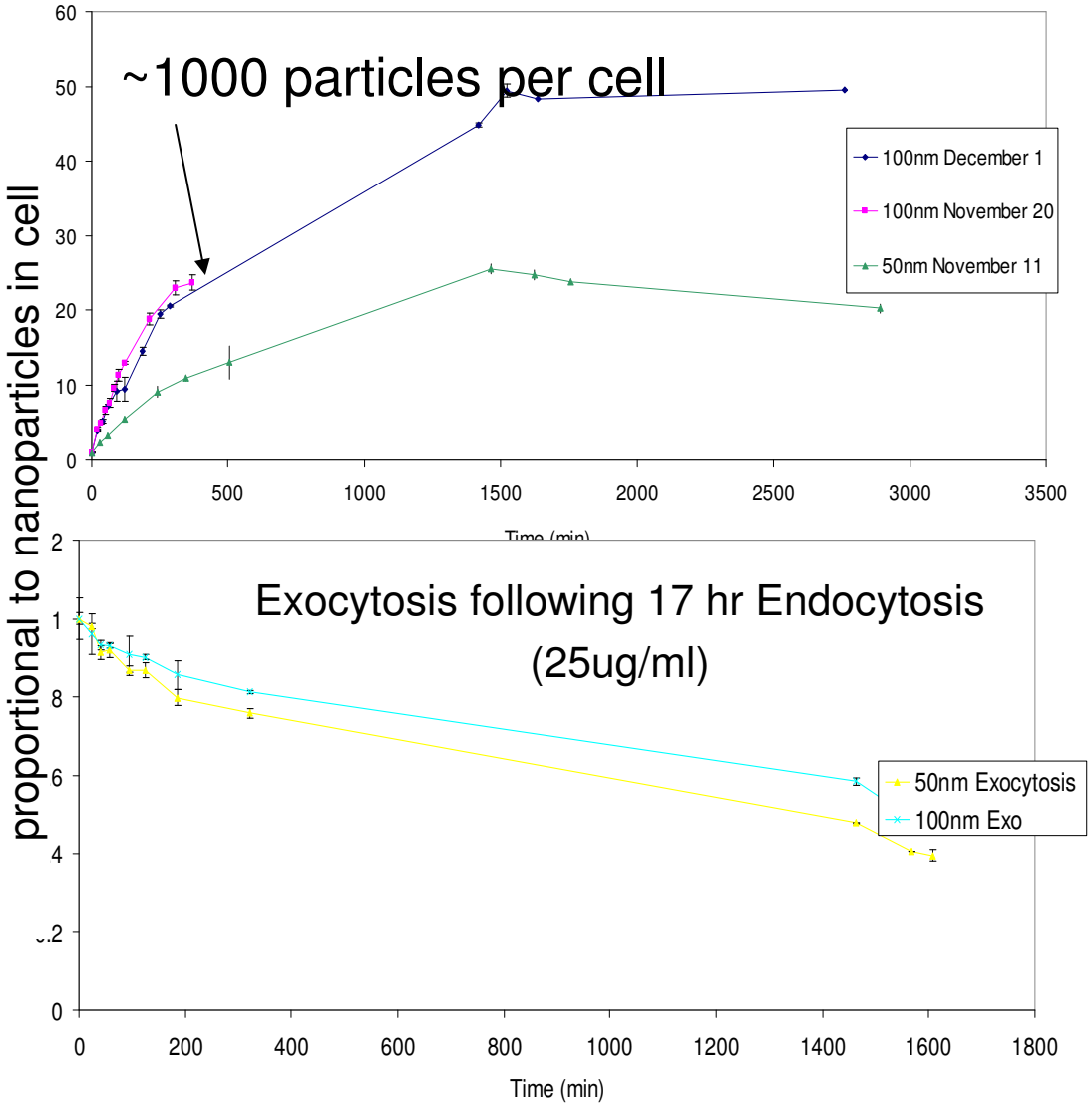

Studies finally reproducible

•Uptake Energy Dependent

•Via endogenous pathways

•Apparent due to cell division in cell lines.

•No Cell level clearance (without exit signal or degradation)

•Accumulation in lysosomes

- •SiO2 Particles (50, 100nm)*
- •A549 lung epithelial cell line

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New tools give unprecedented Assurance of outcomes Many surprises to come

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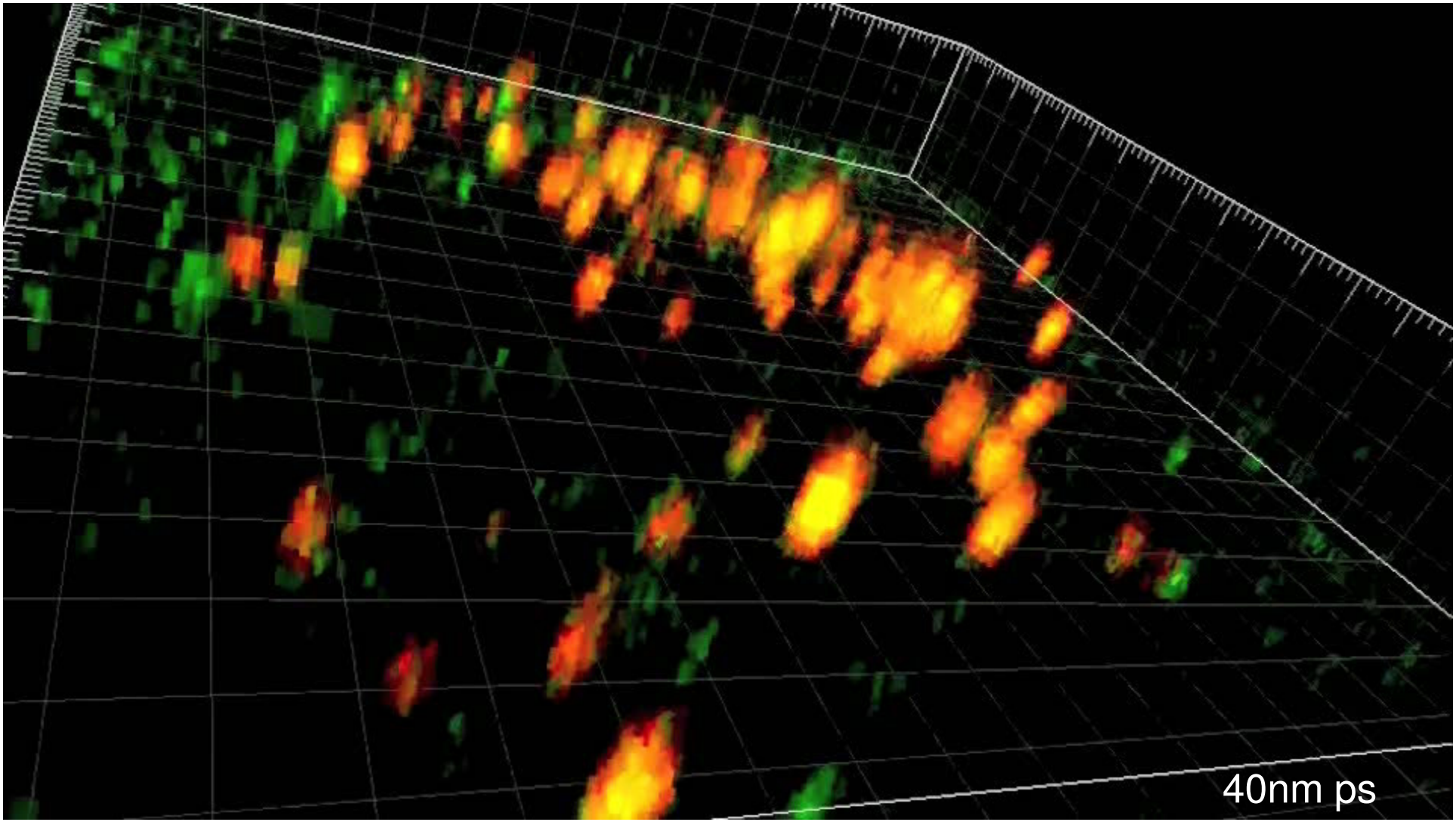

THE CELL (BARRIER ETC) SEES ONLY THE SURFACE-BARE SURFACE IS 'IRRELEVANT'

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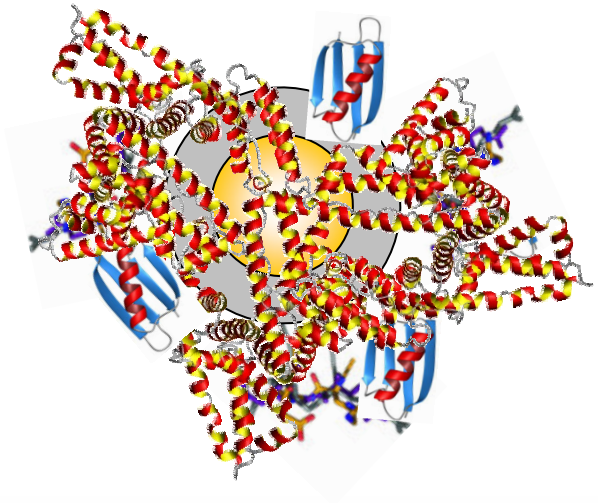
UCD DUBLIN

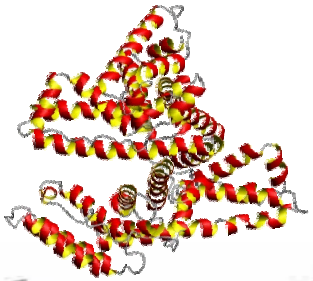
Cozzarelli Prize NAS 2008

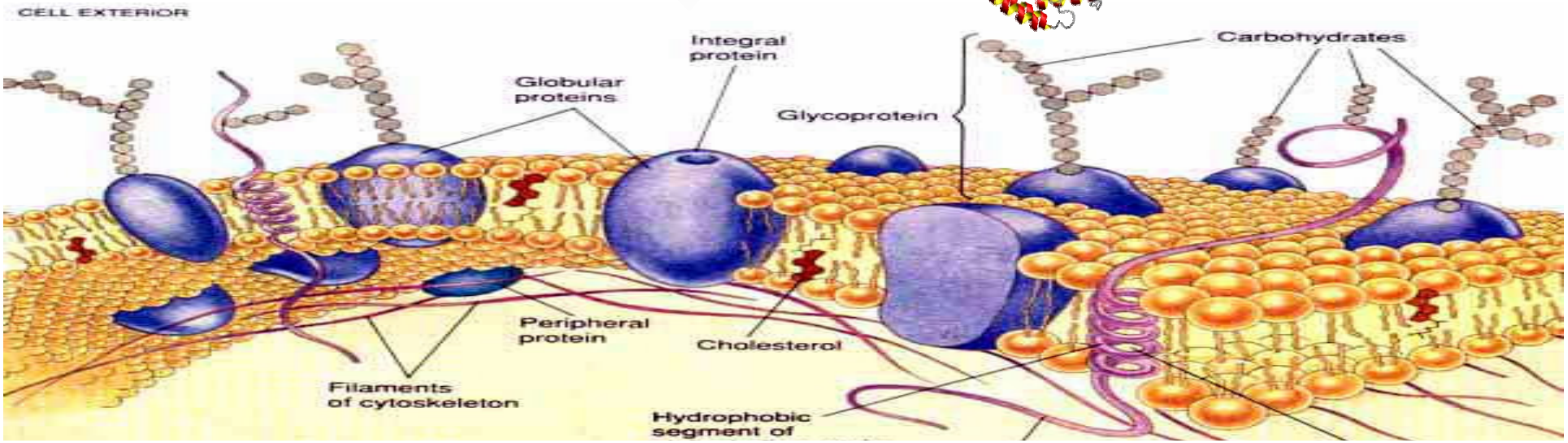
PNAS, 2007, 104, 2050-2055

NATURE NANO, 2009, 4, 546

JACS, 2010







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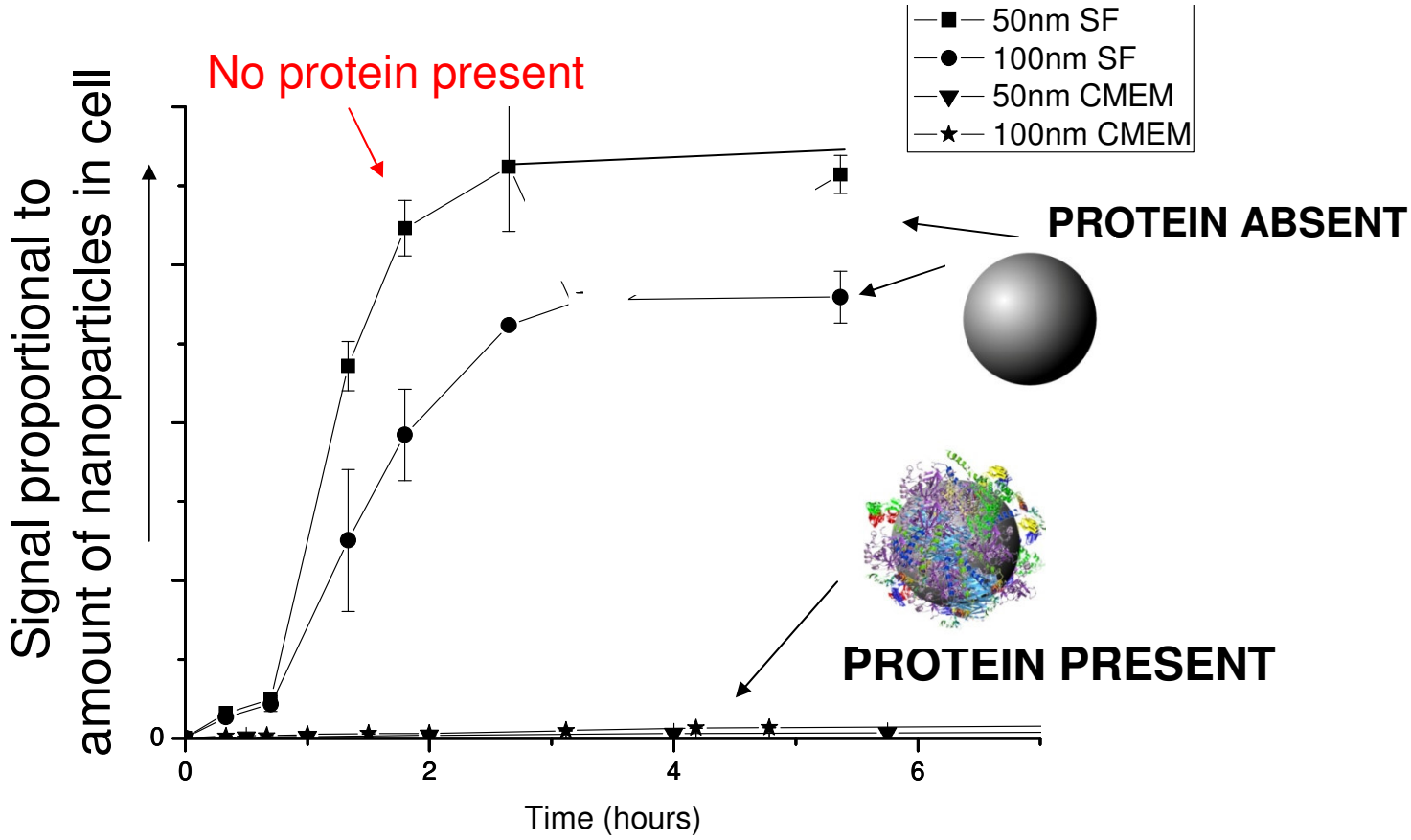
Dramatic effects from adsorbed proteins Medical Devices vs. protein-drug associations?

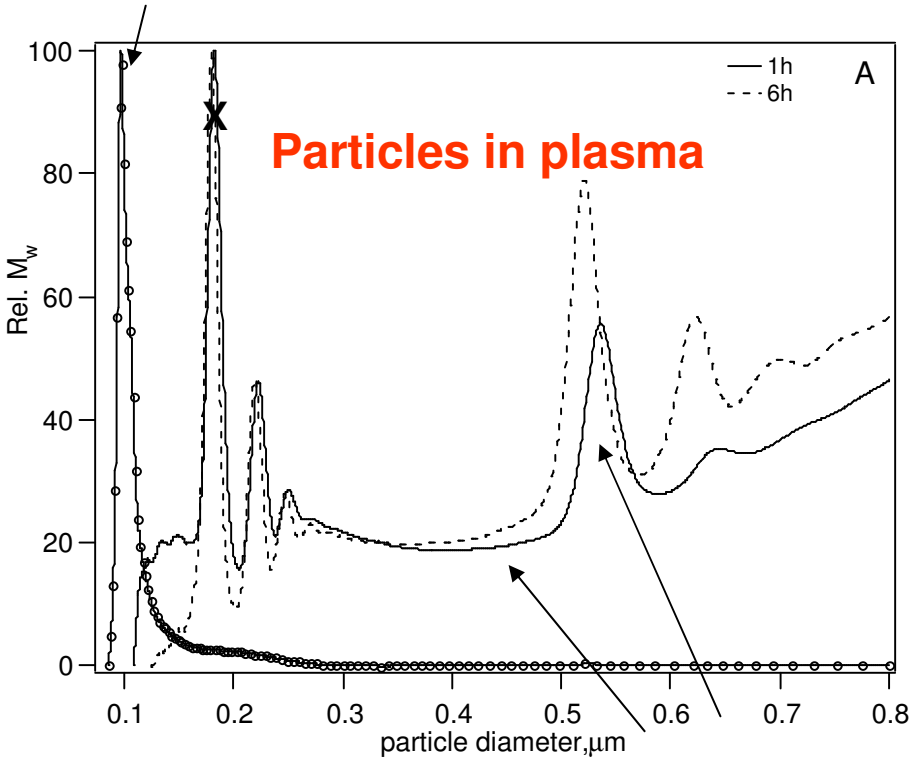


CORONA IS ALWAYS WHAT CELLS/BARRIERS 'SEE'?

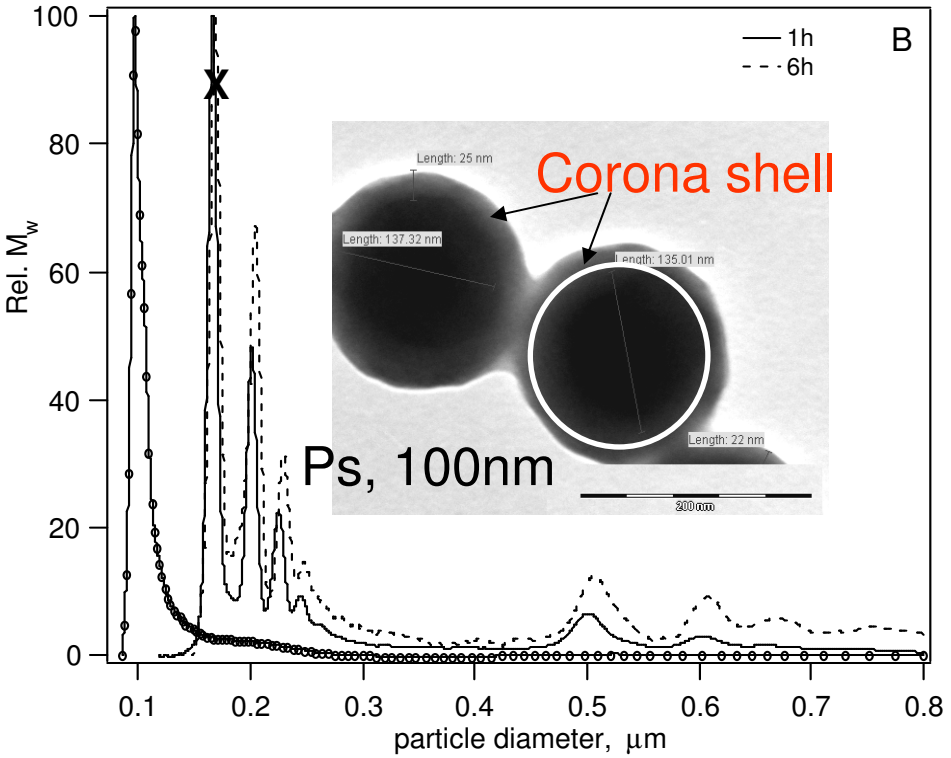
Characterization in Blood (or appropritate Biomedical medium) will be the foundation of all in future Targeting, immune response etc

nanoparticle complexes in situ are essentially the same as when isolated

Bare particles in PBS



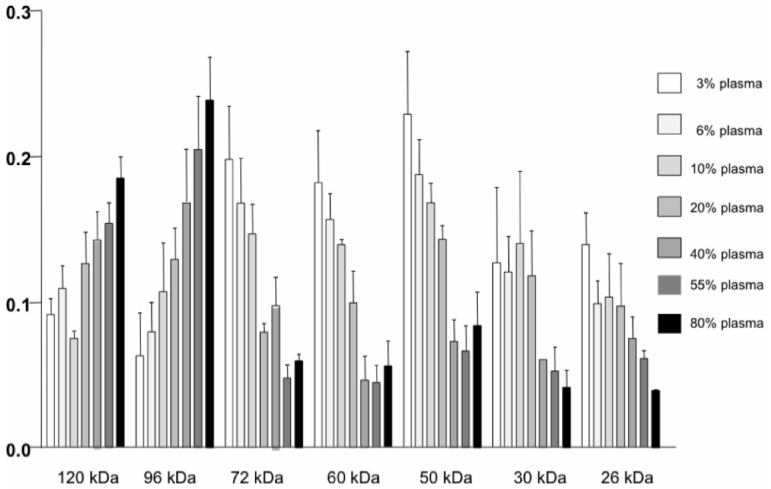
Plasma background

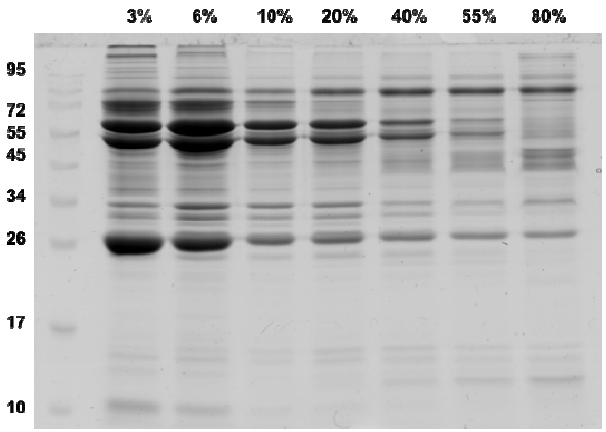


Washed sample, re-suspended

Quantitative Analysis of Corona Identity now Possible;implications profound

Densitometry of SDS-Page Gel





In vitro level, 10%

- Trypsin digestion, peptide extraction and purification on gel slices
- Reverse phase HPLC- MS/MS to ID

Mw	Protein Identity	s.c. [10%]	s.c. [55%]
500 kDa	Apoliprotein-B	282	145
120kDa	Thrombospondin	1	57
90 kDa	Plasminogen	46	94
90 kDa	Transferrin	1	15
90 kDa	Gelsolin	0	18
72 kDa	Fibrinogen alpha chain	651	112
60/72 kDa	Histidine-rich glycoprotein	212	400
72 kDa	Serum Albumin	76	222
72 kDa	Kininogen-1	65	51
60 kDa	Fibrinogen beta chain	841	112
50 kDa	Fibrinogen gamma chain	539	104
50 kDa	Coagulation factor XII	42	90
30 kDa	Apolipoprotein E	55	37
30 kDa	Complement C1q subunit C	30	3
26 kDa	Apolipoprotein A-I	144	123

s.c. = serum concentration

Even the Simplest Materials Can Adopt Unforseen Biological identities In presence of Plasma (CSF, etc) Protein Array Map in plasma

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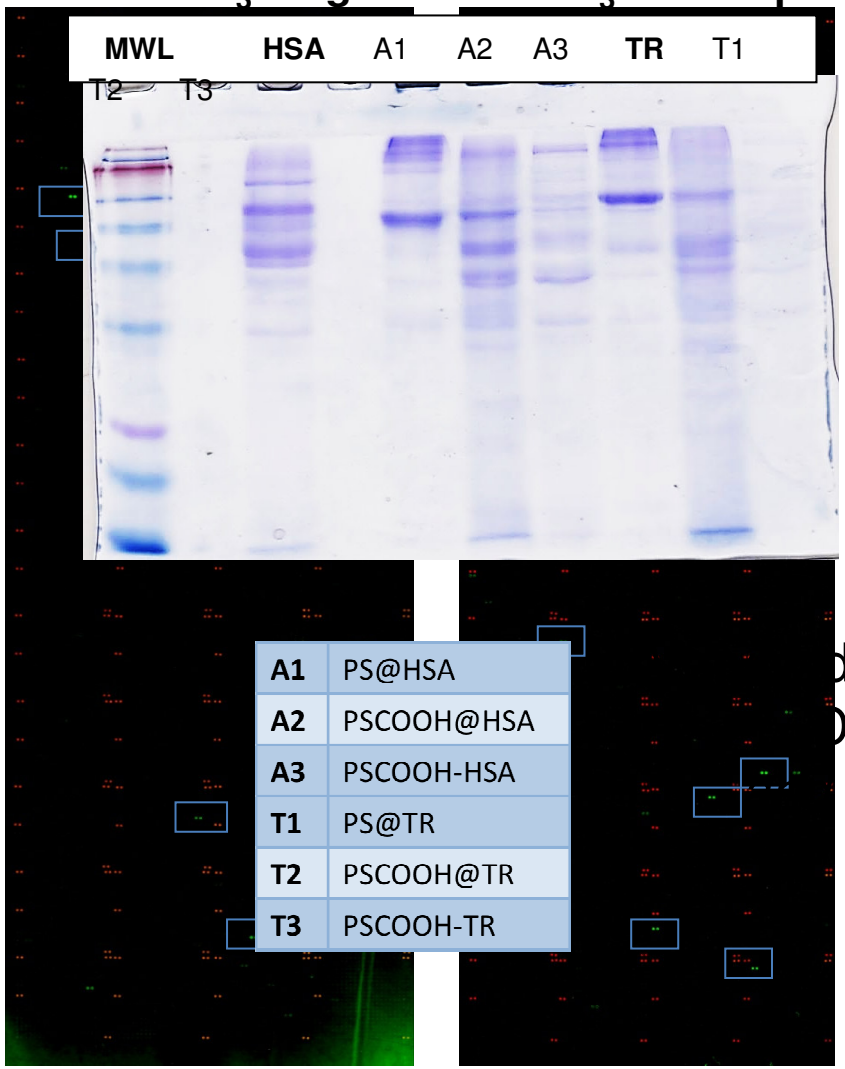
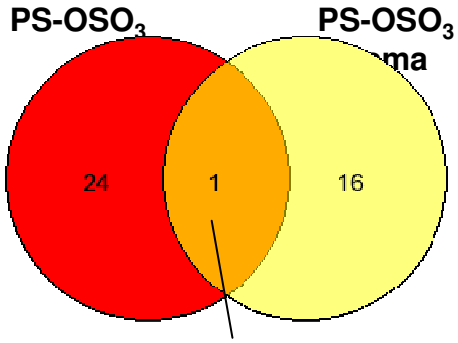
$PS\text{-}OSO_3$ 5mg/ml **$PS\text{-}OSO_3$ in 10% plasma 5mg/ml**

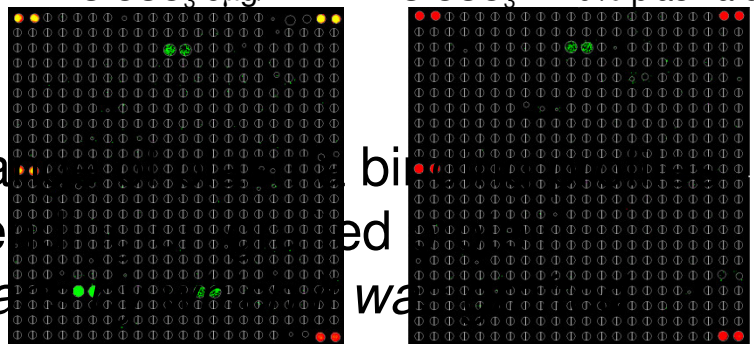




outer dense fiber of sperm tails 2

Block 36

PS-OSO_3 5µg/ml PS-OSO_3 in 10% plasma 5µg/ml



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Multimeric-protein corona assemblies display different interaction pattern than bare NPs- includes functionalized NP's

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Inconsistent Literature?

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In vitro and in vivo comparison

New Tools

Case study of Transferrin

Transferrin (Tf) has target Transferrin receptor (TfR) carries iron into cell
Rapidly dividing tumour cells have need for extra iron (haem)
and cells have overexpressed TfR

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The Complex Role of Multivalency in Nanoparticles Targeting the Transferrin Receptor for Cancer Therapies

Wang et al, J. AM. CHEM. SOC. 2010, *132*, 11306–11313

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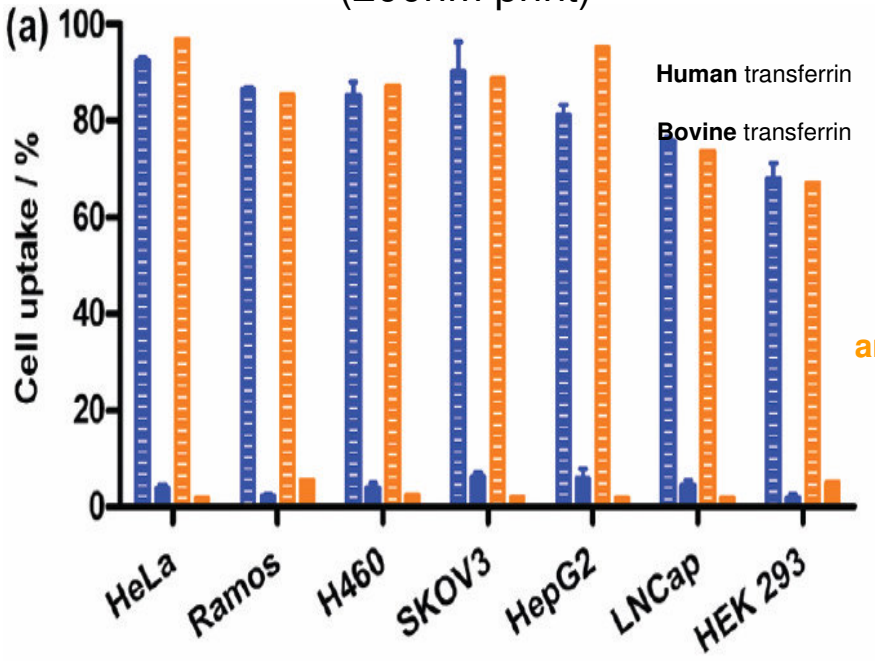
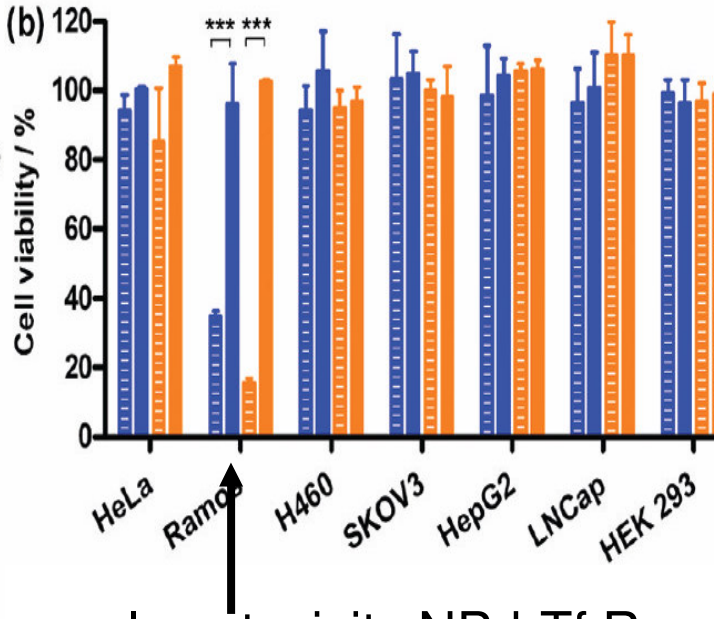
Uptake of X-grafted particles (200nm print)



NP-hTf particles taken up Co-stain acid (lysotracker) non Lysosomal

Viability of Cells (Toxicity)



Anomalous toxicity NP-hTf Ramos
Unchanged with added iron
not iron sponge

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Mechanism of active targeting in solid tumors with transferrin-containing gold nanoparticles
Choi et al PNAS January 19, 107, 1235–1240 (2010)

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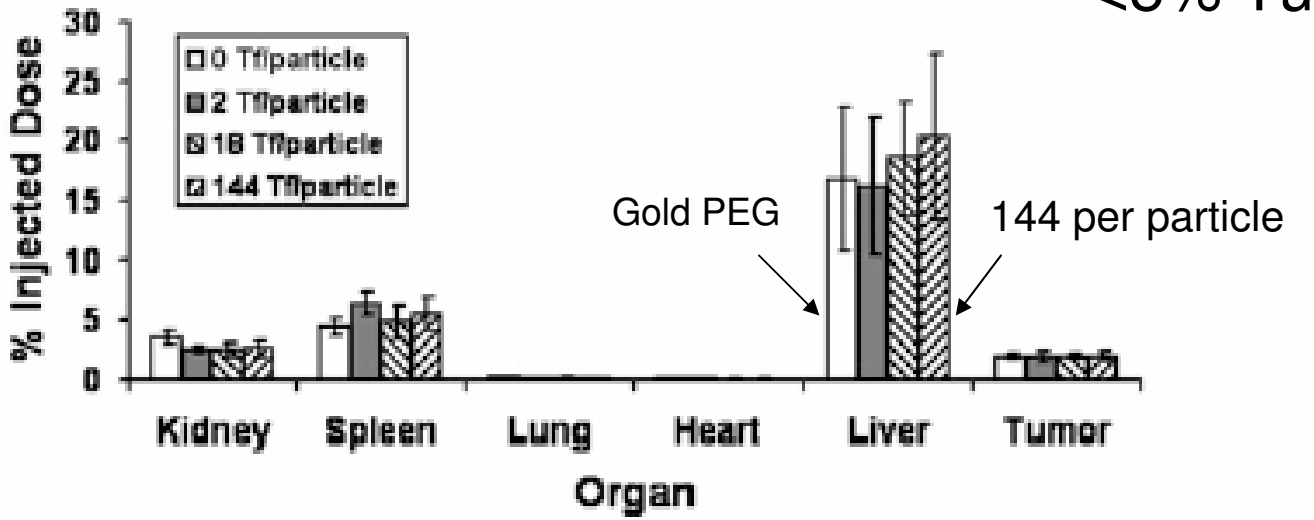
Typical, 25-40% res
<5% Tumor



- 24 hours after i.v. tail injection mic with Neuro2A tumours
- Targeting does not change the bulk balance of particles in organs (or tumour)
- Most goes to RES (many in Kupfer cells of liver)
- Within organs uptake of particles in Tf rich cells (eg Tumour) *threshold 144*

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COMMUNICATING WITH THE MACHINERY OF THE CELL-THE REAL INTERFACE

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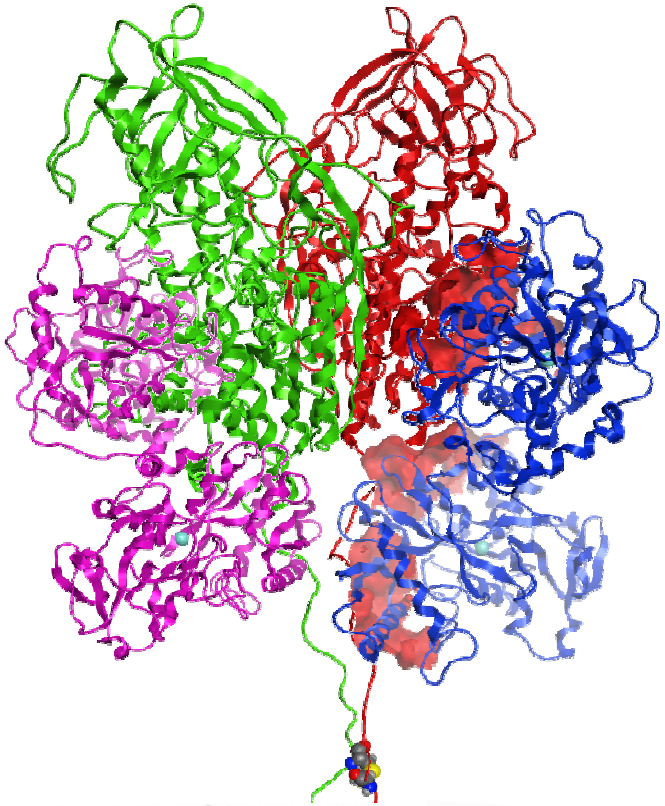

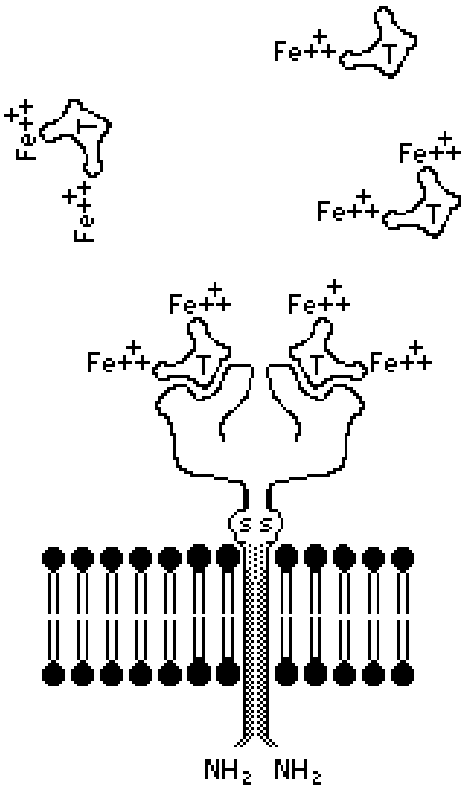

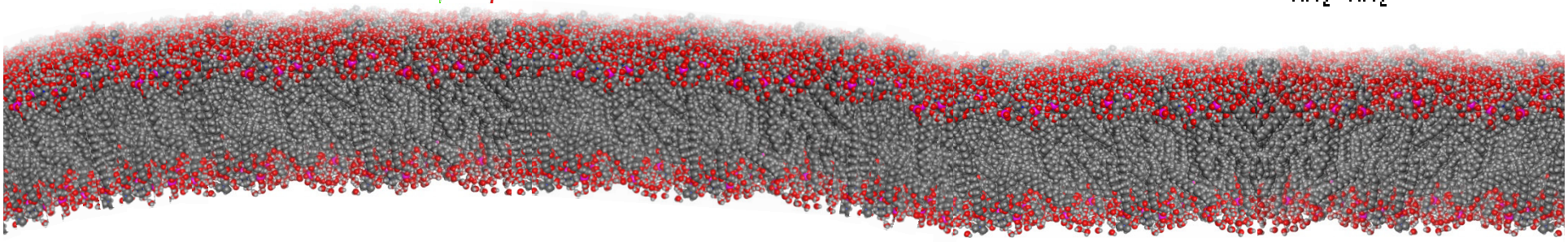

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GRAFTING OF PROTEINS, ORIENTATION, DISRUPTION INTERACTION WITH PROTEINS OF ENVIRONMENT

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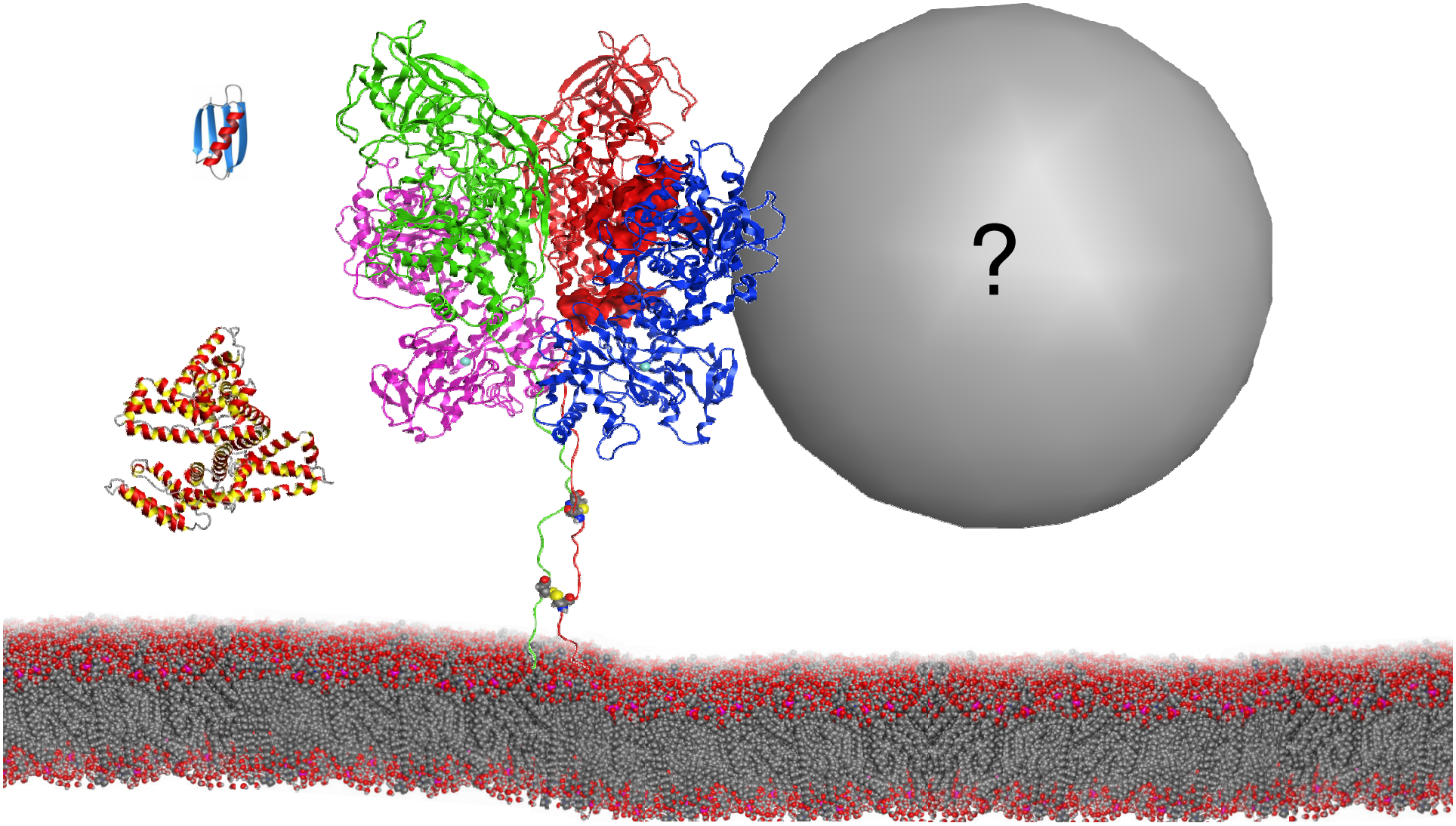

Silencing Transferrin receptor
For Many Examples cited in literature,
Silencing pathway does not stop their uptake
Are we REALLY seeing simple Targetting

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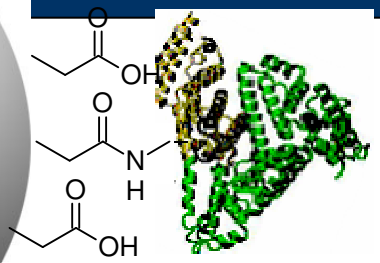
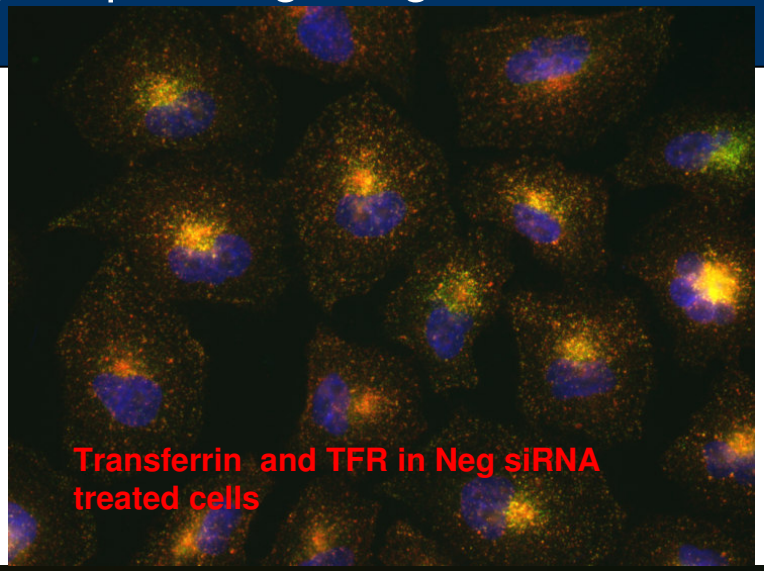
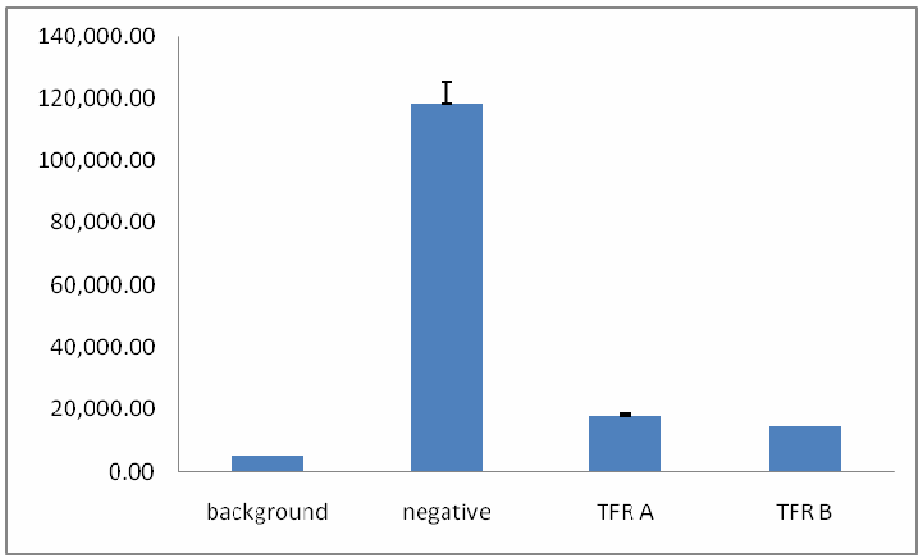


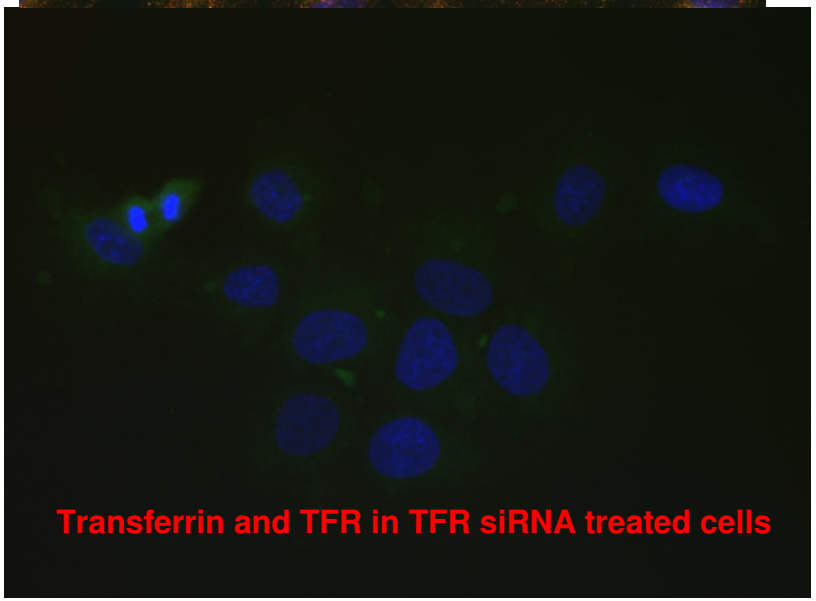
Red: TFR
Green: transferrin



Binding Transferrin on NPs

Very strong decrease in Tf uptake





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Some Messages

UCD DUBLIN

- NEW METHODS OF IN-CELL, IN VIVO IMAGING CRITICAL FOR NANOMEDICINES(OLDER ESTABLISHED METHODS ICPMS ETC UNSUITED)

- CHARACTERIZATION IN SITU IN BIOMEDICAL CONTEXT-NEW METHODS, PROTEOMICS BROADLY DEFINED

- RADICAL RE-THINK OF TARGETING, WHAT IS HAPPENING, AND WHAT WILL BE REQUIRED FOR DURABLE AND SAFE APPLICATION-**ENGINEER THE INTERFACE, DON'T GUESS!**