Nanotechnology

NCI Alliance for Nanotechnology in Cancer

Nanotechnology for medical applications: benefits, concerns and effects on the immune system

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NATIONAL CANCER INSTITUTE

Frederick National Laboratory for Cancer Research

Outline

Presentation outline

NCL Nanotechnology Characterization Laboratory | NCI Alliance for Nanotechnology in Cancer

- Nanotechnology Definitions
- Nanoparticles in Daily Life
- Nanoparticles in Medical Applications
- Nanoparticles for Cancer Diagnosis and Therapy
  - Benefits of nanotechnology
  - Toxicity concerns
- Nanomaterials and the Immune System

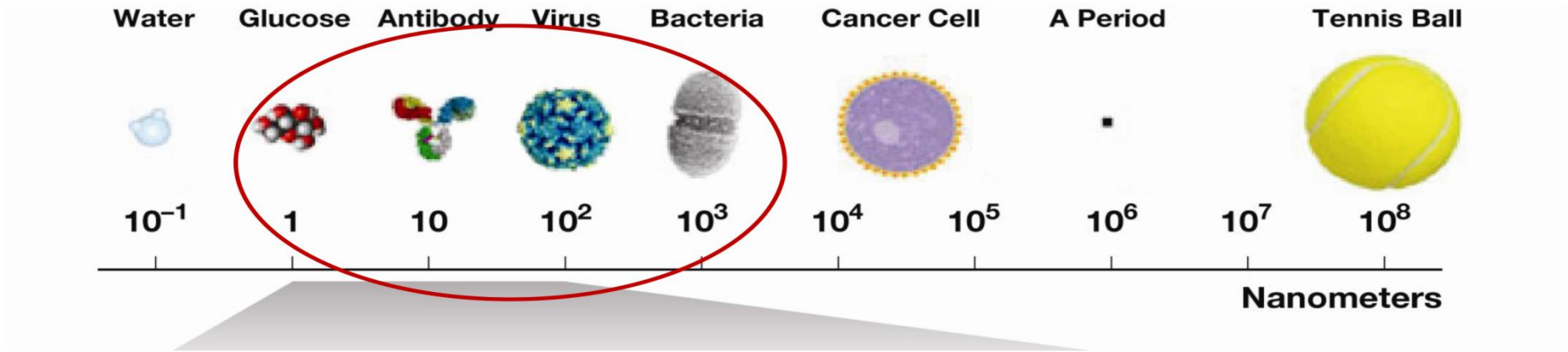
What is nano?

What is Nano?

Nanotechnology:

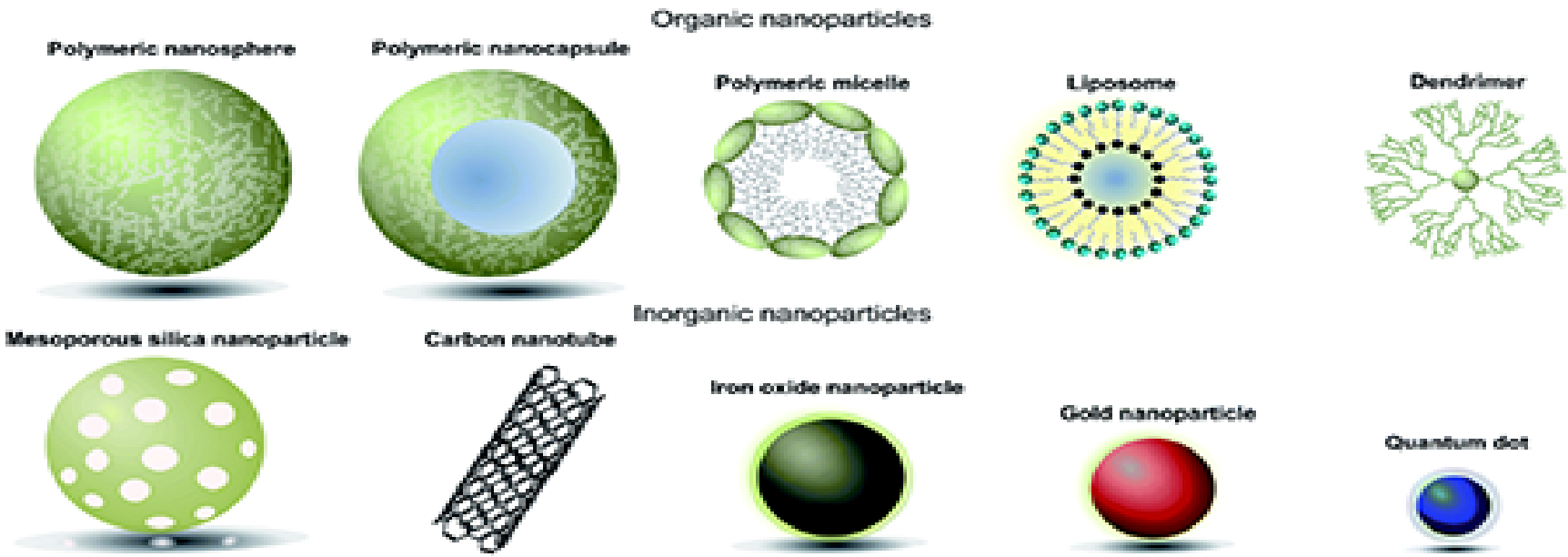
"Research and technology development at the atomic, molecular or macromolecular scale leading to the controlled creation and use of structures, devices and systems with a length scale of approximately 1 – 100 nanometers (nm)." (Source: National Nanotech Initiative)

"Whether a material or end product is engineered to exhibit properties or phenomena, including physical or chemical properties or biological effects, that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to one micrometer (1,000 nm)"(US FDA)



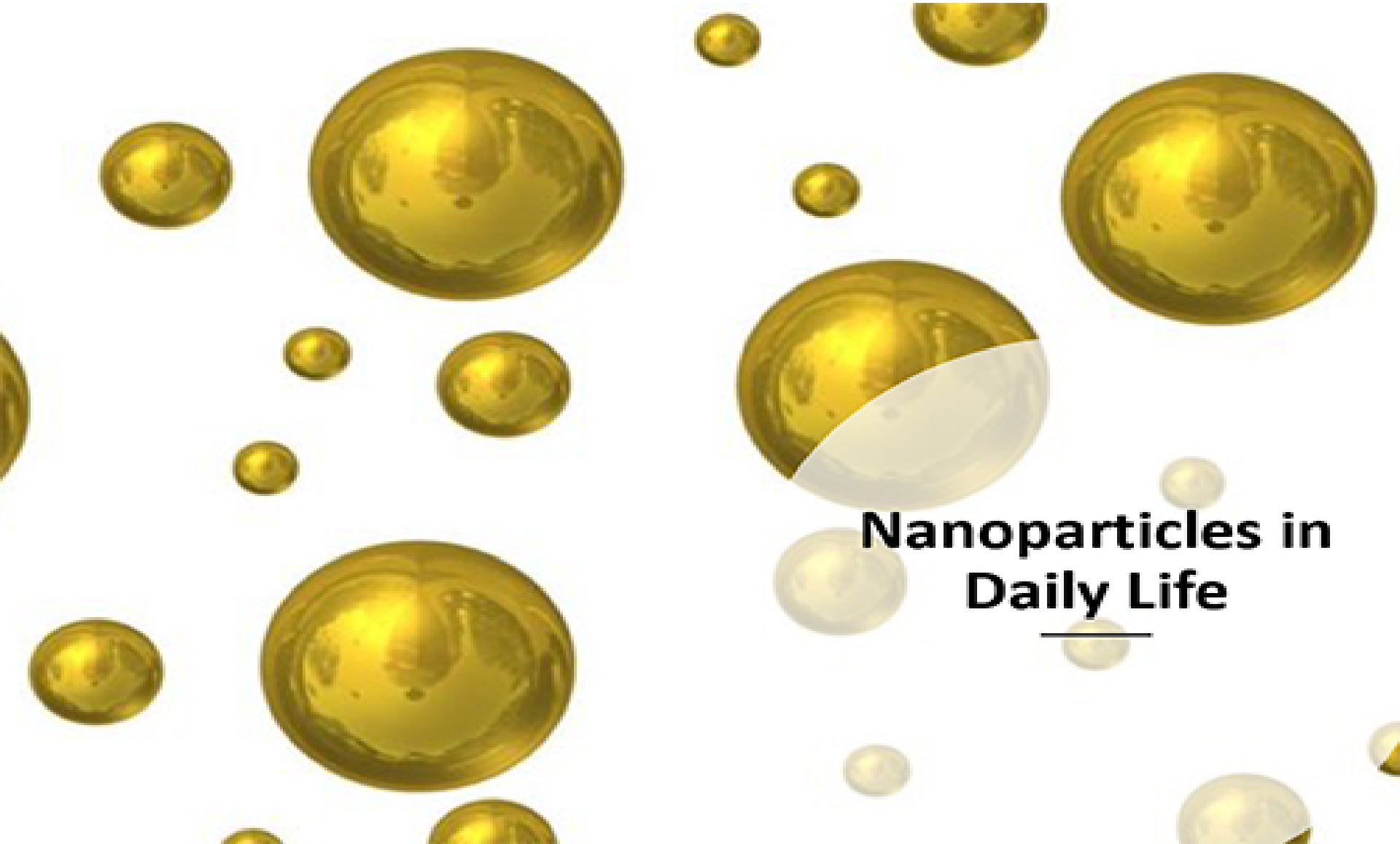
Examples of nanomaterials

Examples of Nanomaterials



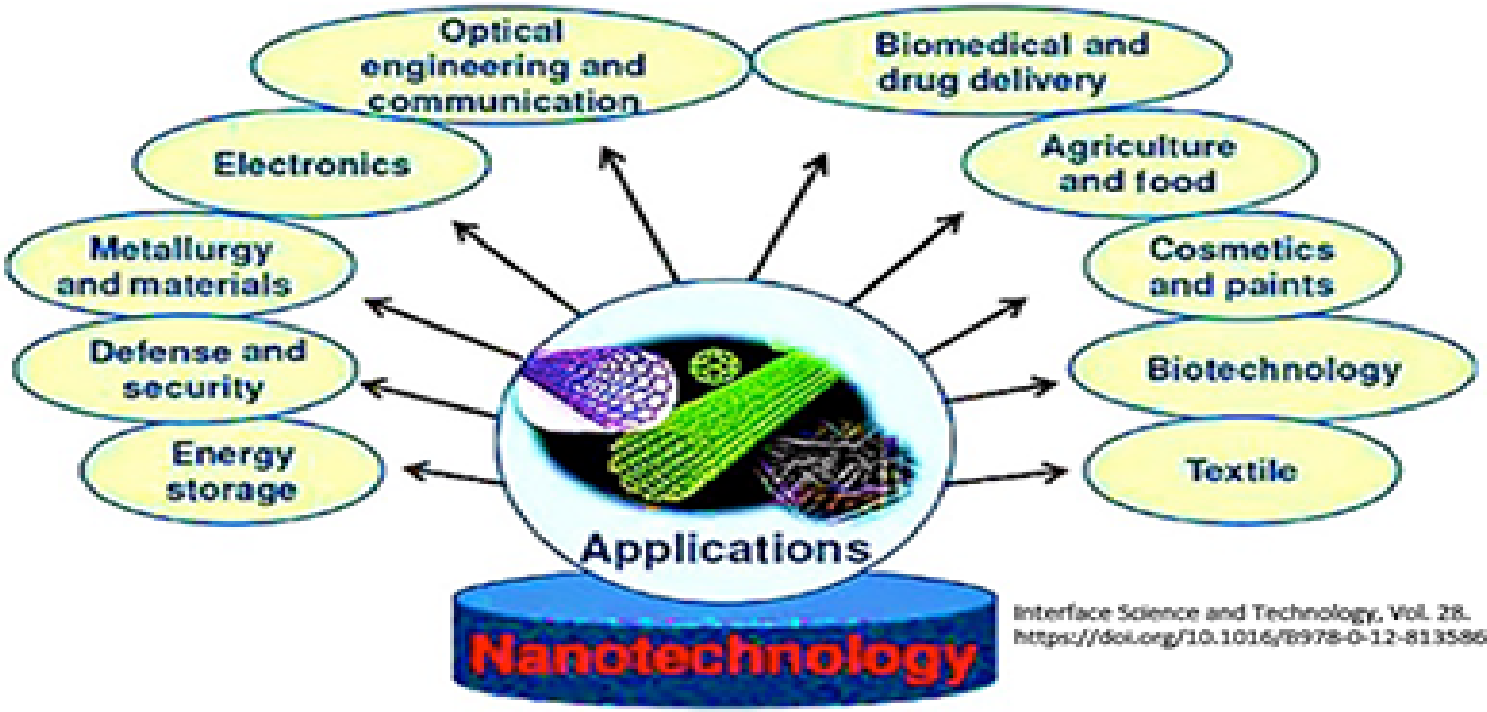
Richards D.A., Chem. Sci., 2017, 8, 63

Nanoparticles in daily life

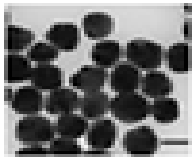


Nanoparticles

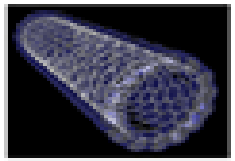
Nanoparticles in Daily Life



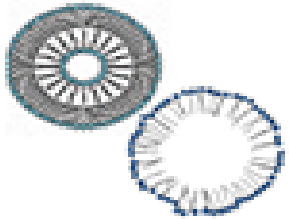
Interface Science and Technology, Vol. 28.
https://doi.org/10.1016/B978-0-12-813586-0.00004-3



Silver nanoparticles are used as anti-microbial materials



Carbon nanotubes are used as structural materials



Liposomes and emulsions are commonly used in cosmetics

Sunscreens contain nanoscale **TiO_2 or ZnO_2**

Products

Examples of products containing nanomaterials

Chantecaille Nano Gold Energizing Cream	**Trucare Nano Silver Toothpaste Anti Bacterial, Fights Ulcers Canker Sore**	**Melaklear Nano Alpha Arbutin Anti Melasma Spots SPF20 Skin Lightening Cream**
Research In Beauty Nano-Complex Keratin Gold Shampoo	**Acz Nano Zeolite Extra Strength-Detoxification Supplement**	**Cyclic Nano Silver Cleanser Soap**

Source: Gupta&Xie, *Journal of Environmental Pathology, Toxicology and Oncology*, 37(3):209–230 (2018)

Products

Examples of products containing nanomaterials

Companies and nanotechnology

> 800 companies worldwide use nanotechnology

Nanotechnology Products, Applications & Instruments

(Links listed alphabetically)

A | B | C | D | E | F | G | H | I | J | K | L | M | N | O | P | Q | R | S | T | U | V | W | X | Y | Z | All

Showing results **1 - 25** of **898**

Ångström Aerospace Corporation (Sweden)

Ångström Aerospace Corporation mission is to develop and provide products, including services based on state-of-the-art Micro-ElectroMechanical Systems (MEMS) and nanotechnologies. Using advanced 3-dimensional wafer level packaging, Ångström Aerospace enables 3D-System-in-Package modules that enables unprecedented possibilities to combine micro-electronics and MEMS sensors/actuators.

10 Angstroms (USA)

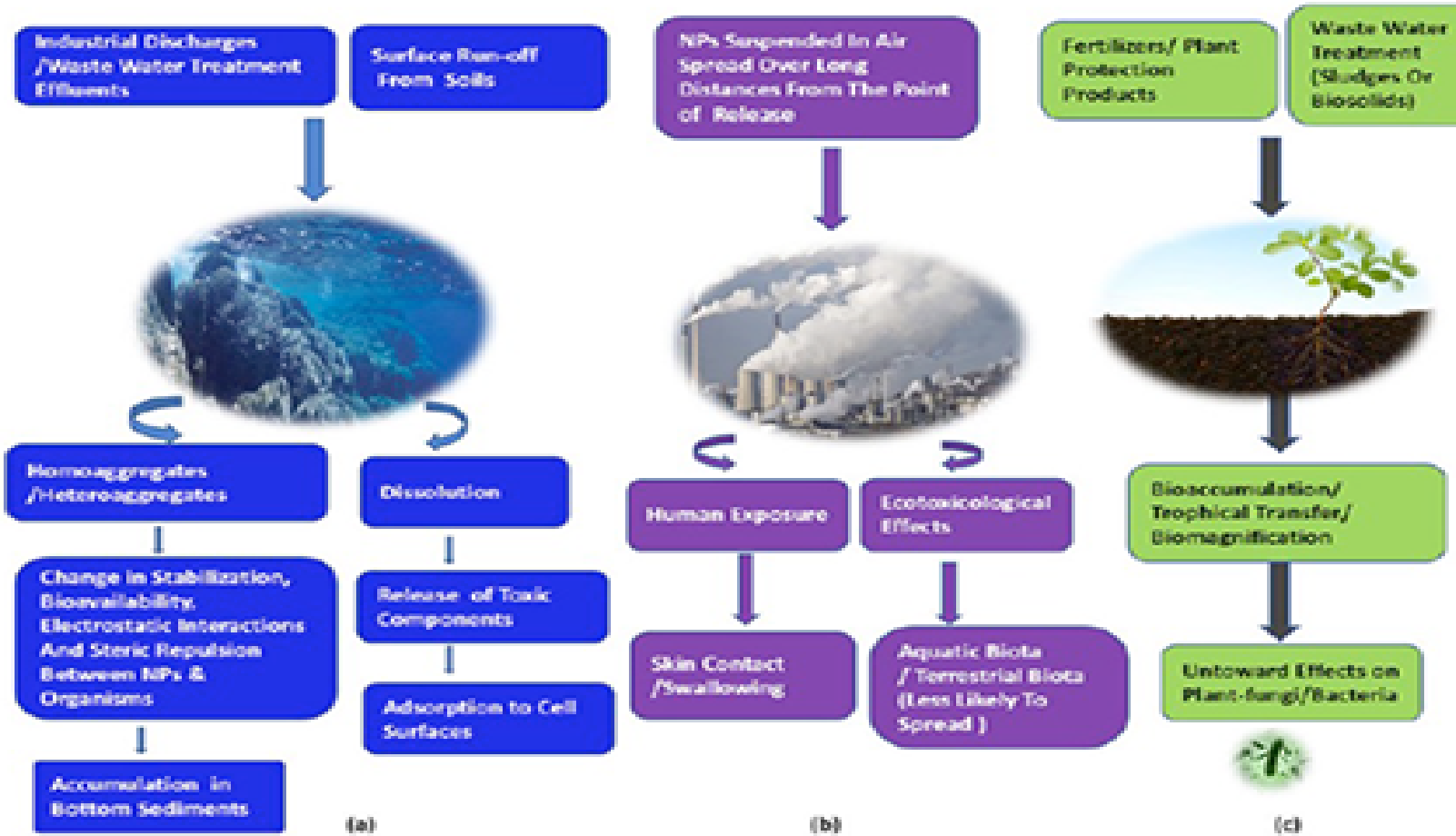
10 Angstroms is dedicated to bringing innovative systems and equipment to the nanotechnology R&D market. The company provides both sales representation and servic for advanced instrumentation companies.

Never
Subscr
get all

https://www.nanowerk.com/nanotechnology/nanomaterial/products_a.php

Nanomaterials

Industrial and Environmental nanomaterials



Source: Gupta&Xie, *Journal of Environmental Pathology, Toxicology and Oncology*, 37(3):209–230 (2018)

Nanoparticle exposure

Potential Routes of Nanoparticle Exposure

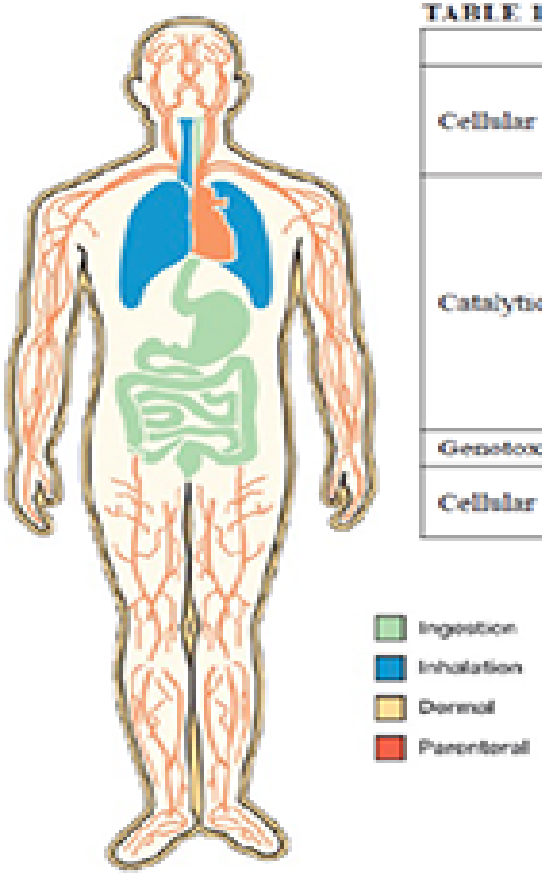


TABLE 1: Mechanisms of engineered nanoparticle toxicity

Mechanisms of toxicity		Reference number
Cellular uptake	Direct intracellular entry	119
	Cell membrane binding	120
	Uptake through reticuloendothelial system	121
Catalytic activity	Release of more reactive ionic form from nanoparticle surface	60
	ROS generation, oxidative stress	24, 122
	Lipid peroxidation	32, 34
	Protein denaturation	123
	Inflammation	35, 124
	Endothelial dysfunction	125
	Mitochondrial perturbation	126
Genotoxicity	DNA damage, mutations	33, 48, 127
Cellular dysfunction	Phagocytic function impairment	128
	Altered cell cycle regulation	36

Source: Gupta&Xie, *Journal of Environmental Pathology, Toxicology and Oncology*, 37(3):209–230 (2018)

- Exposure to industrial and environmental nanomaterials may impact human health
- Many reports in the current literature about mechanisms of nanoparticle toxicity

Source: Stern ST.&McNeil S., TOXICOLOGICAL SCIENCES 101(1), 4–21 (2008) doi:10.1093/toxsci/kfm169

Nanoparticles for medicine

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Medical applications

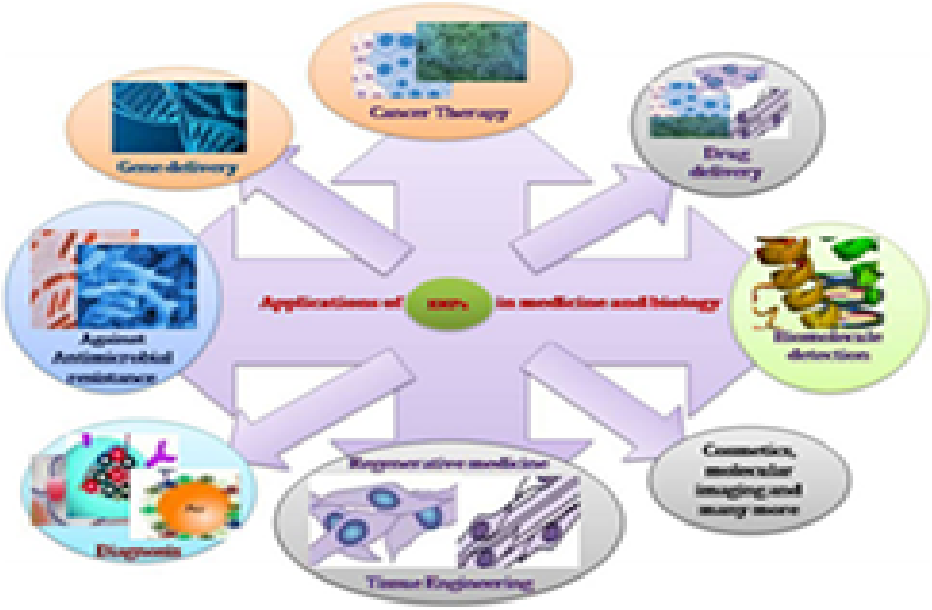
Nanoparticles for Medical Applications

Properties attractive for medical applications

- Improve solubility of hydrophobic drugs
- Multifunctional capability
- Target tissues and cells affected by disease

Applications

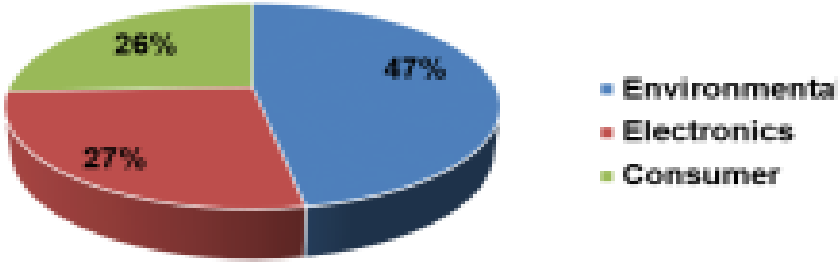
- Gene therapy
- Drug delivery
- Immunotherapy
- Tissue engineering
- Diagnostics
- Devices
- Image-guided surgery
- Imaging agents

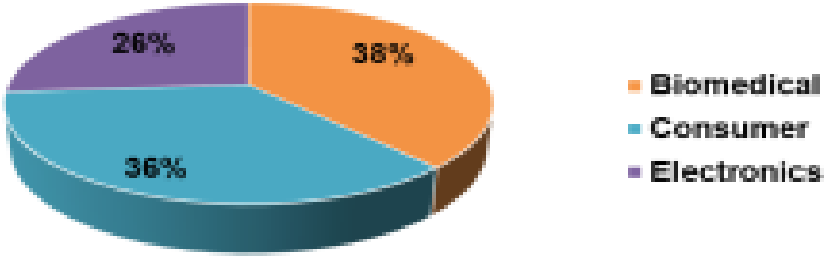


Rudramurthy, G. R. and M. K. Swamy (2018). BioC Journal of Biological Inorganic Chemistry 23(8): 1185-1204.

Evolving landscapes

Evolving Landscape of Nanotechnology Products

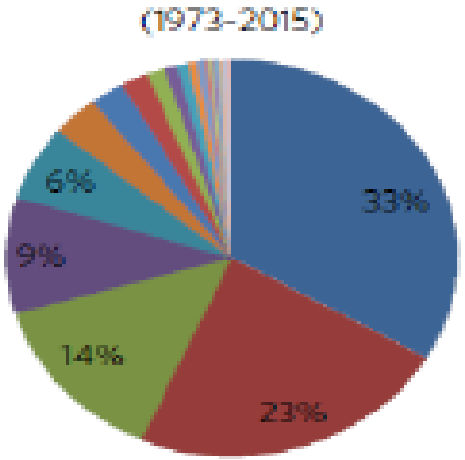




These graphs are prepared based on the business analytical report by Cumming L., BCC Research (201

Global Nanotechnology Market in 2015 was dominated by environmental, electronic and consumer products

Biomedical Applications of Nanotechnology are predicted to have the highest 5-year compound annual growth rate by 2021



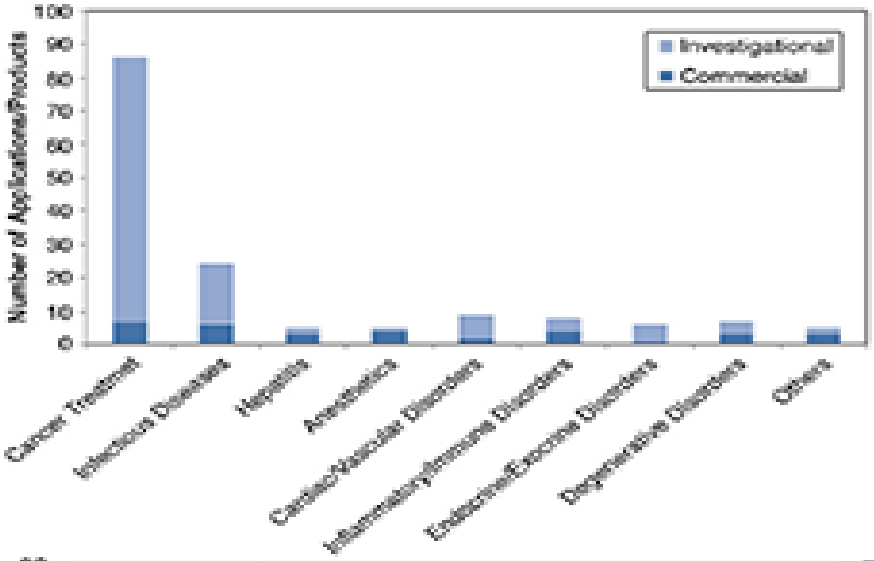
- Liposome
- Nanocrystal
- Emulsion
- Iron-polymer complex
- Micelle
- Drug-protein complex
- Drug-polymer complex
- Dendrimer
- Polymeric NP
- Nanobubble
- Silica NP
- Drug-lipid complex
- Drug-metal complex
- Protein NP
- Drug NP
- Solid lipid NP
- Nanotube
- Metal-protein complex
- Metal-nonmetal complex
- Metal-polymer complex

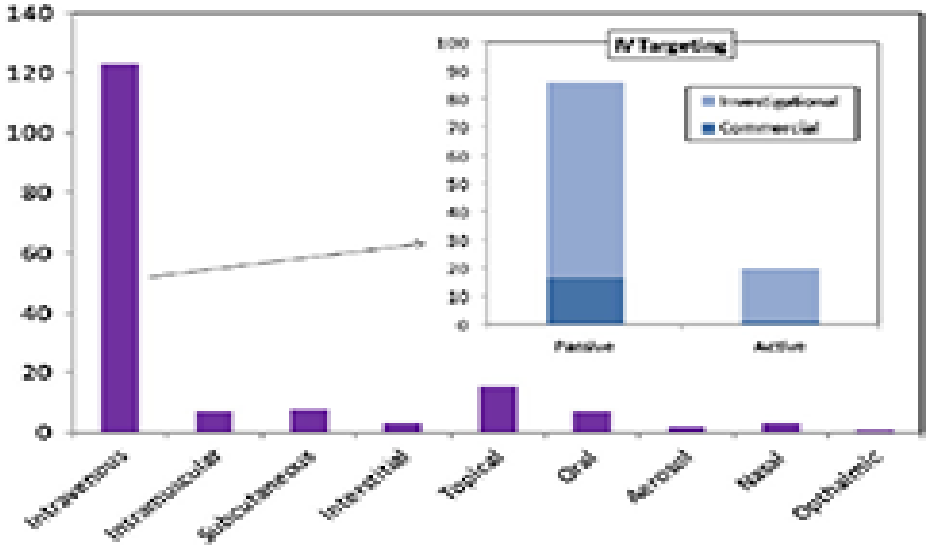
D'Mello S.R. et al., Nature Nanotechnology, June 2017

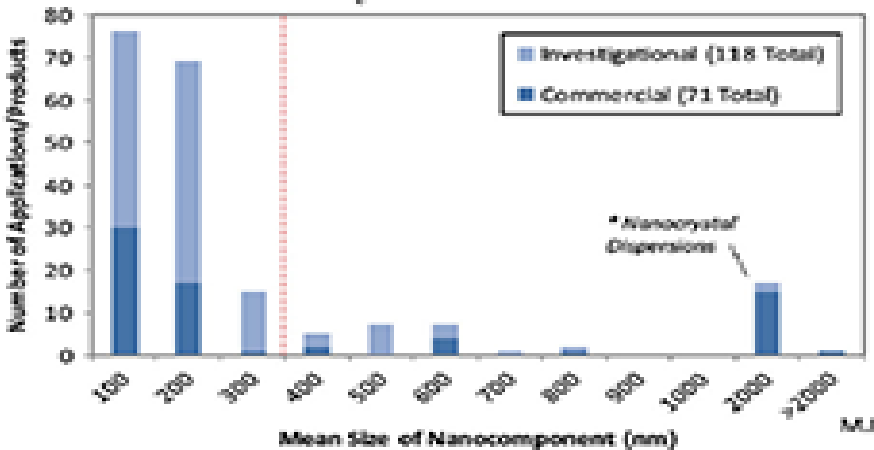
Liposomes, Nanocrystals and Emulsions dominate current nanomedicine landscape

Medical applications

Nanoparticles in Medical Applications







Common features of Nanomedicines:
- Primary market is cancer therapy
- Intravenous administration
- <350 nm in size
- Neutral, hydrophilic surfaces
- Spherical

M.L. Etheridge et al / Nanomedicine: Nanotechnology, Biology, and Medicine 9 (2013) 1–14

Clinical grade products

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Examples of Clinical Grade Nanotechnology Products

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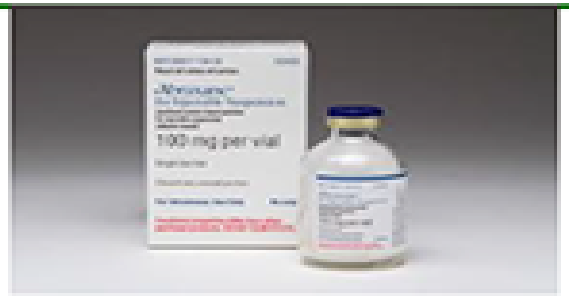

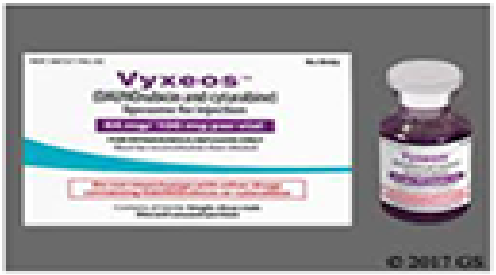

Nanoproducts

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Examples of Clinical Grade NanoProducts

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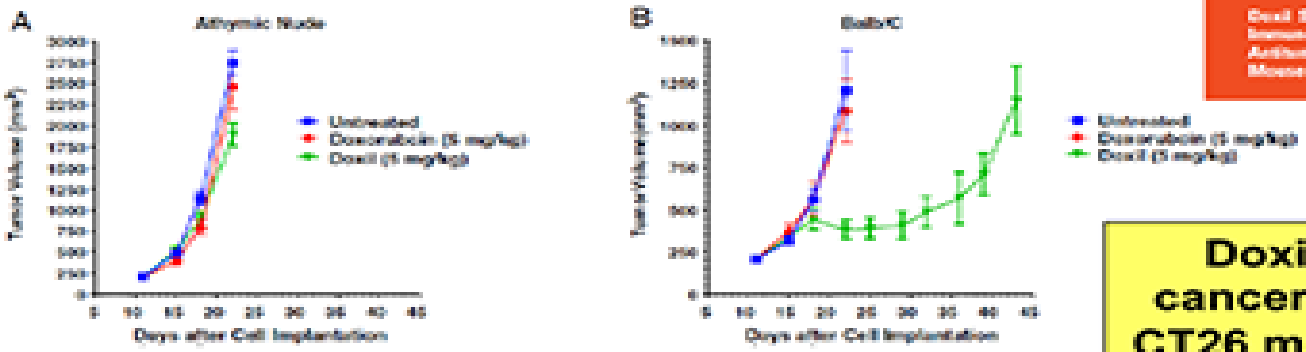
Immunotherapy

Benefits: Immunotherapy



Doxil improves efficacy of cancer immunotherapeutics in CT26 mouse model of colorectal cancer

The Immunotherapy Opdivo & Abraxane for Recurrent HER2-Negative Metastatic Breast Cancer

A Phase 1, Open-Label, Multicenter, Safety Study of Nivolumab (BMS-936558) in Combination With Nab-Paclitaxel Plus or Minus Gemcitabine in Pancreatic Cancer, Nab-Paclitaxel / Carboplatin in Stage IIIB/IV Non-Small Cell Lung Cancer or Nab-Paclitaxel in Recurrent Metastatic Breast Cancer (NCT02309177)

Abraxane is investigated in combination with a-PD-1 in clinical trials for metastatic breast cancer

Benefits: Gene therapy

Benefits: Gene therapy

Alnylam PHARMACEUTICALS

Transthyretin (TTR) is a protein primarily made in the liver

A genetic mutation in the TTR gene causes the **TTR protein to form clusters known as amyloid deposits**

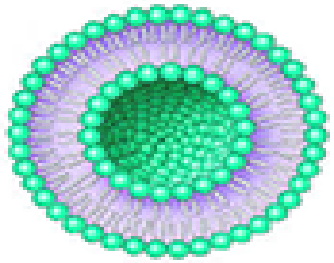
Amyloid deposits build up in different parts of the body, leading to symptoms of hATTR amyloidosis

https://www.onpattro.com/how-onpattro-works

Benefits: Vaccines

Benefits: Vaccines

PDS Biotechnology



PDS0101/Versamune®

Mechanism of Action:

- Activates Both CD4+ and CD8+ T-cells
- Stimulates Type I interferon response
- Alters tumor micro-environment

Product	Indication	Partner	Combination	Status
PDS0101 (HPV-Cancer)	Head & neck cancer First line treatment Recurrent/metastatic	MERCK	KEYTRUDA®	Initiate Phase 2 1Q 2020*
	Advanced HPV cancers	NIH National Cancer Institute	Novel Immunotherapies	Initiate Phase 2 1Q 2020*
	Cervical cancer Stage IIb-IVa		Chemo-radiotherapy	Phase 2 ready

- Nanoparticles (lipoplexes, polyplexes, liposomes) were shown to improve vaccine efficacy
  - One example of such platforms is shown on this slide
  - Versamune platform is being explored for combination therapies

Benefits: Lymphatic delivery

Benefits: lymphatic delivery

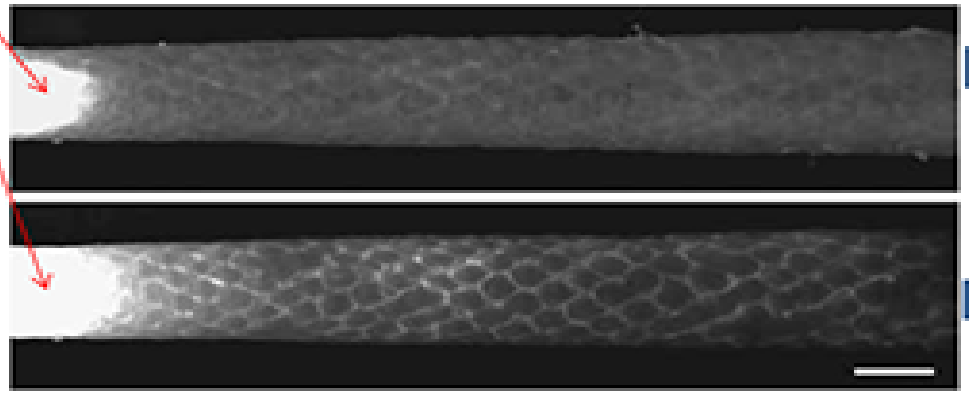
- i.d. injection
- Examine draining lymph nodes

Injection Site

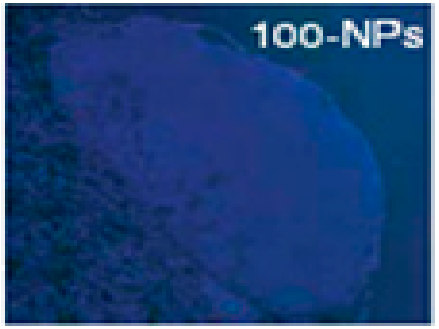
Tail

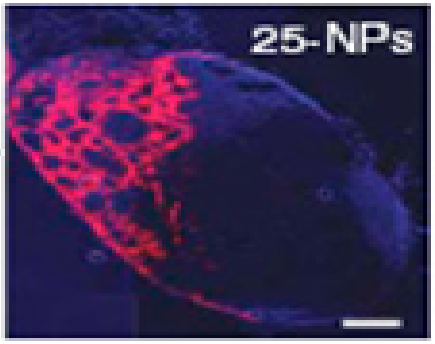
100nm

25nm



Draining lymph nodes





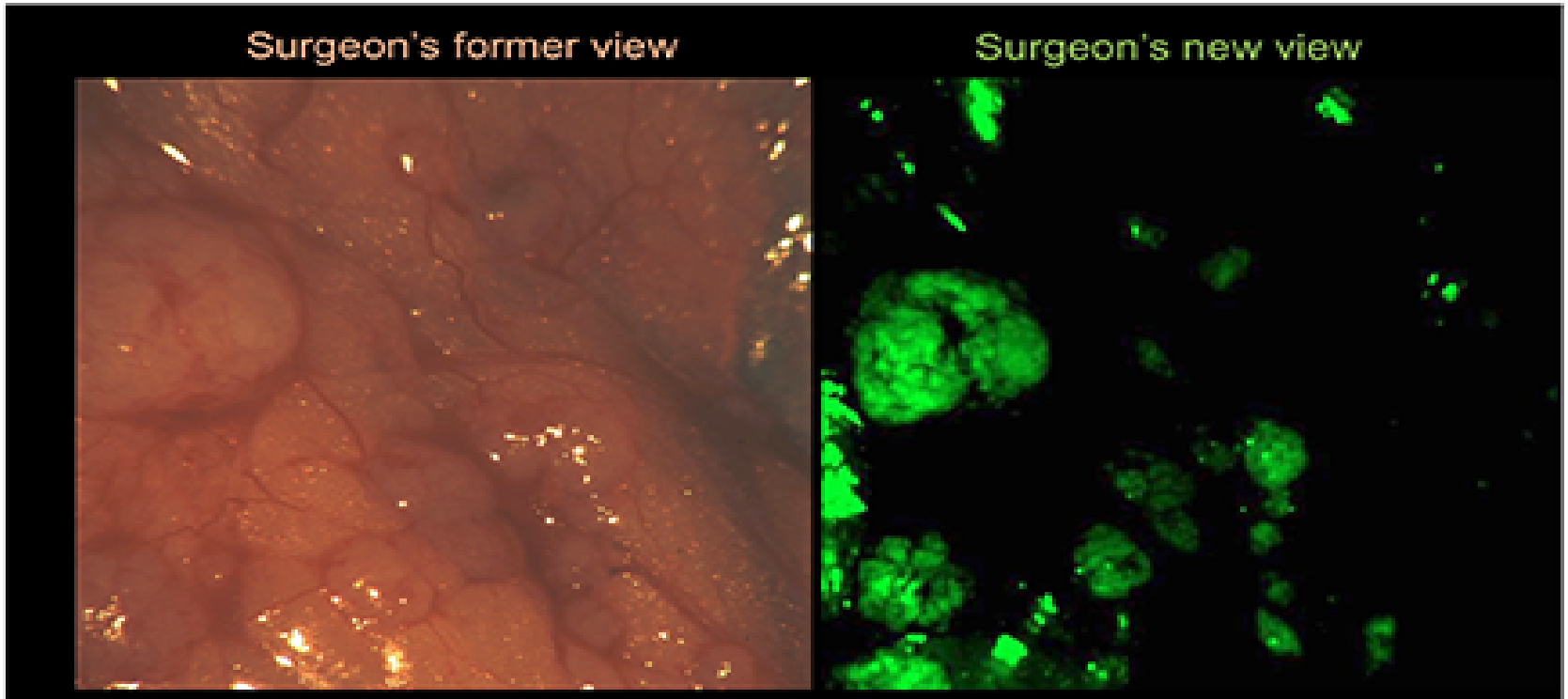
Smaller particles travel through lymphatics. Larger particles do not.

Reddy ST et al, and Hubbell JA. (2007) Nature Biotech., 25 (10):1159-1164

- **Particle distribution to lymph nodes after i.d. injection depends on their size**
- **Lymphatic delivery benefits vaccines, HIV and infectious diseases therapy**

Benefits: Image guided surgery

Benefits: image guided surgery

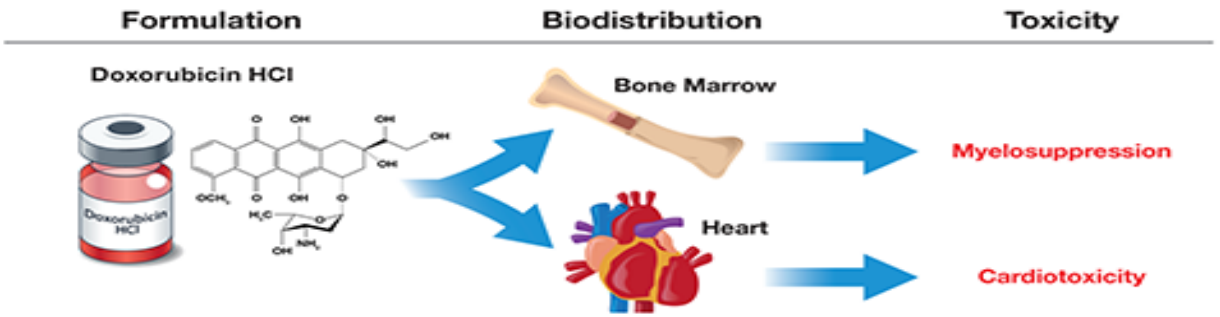


View of localized region in peritoneal cavity of an ovarian cancer patient as seen with the naked eye (left) or with the aid of a tumor-targeted fluorescence dye (right).

https://medicalxpress.com/news/2011-09-technology-fluorescence-guided-ovarian-cancer-surgery.html

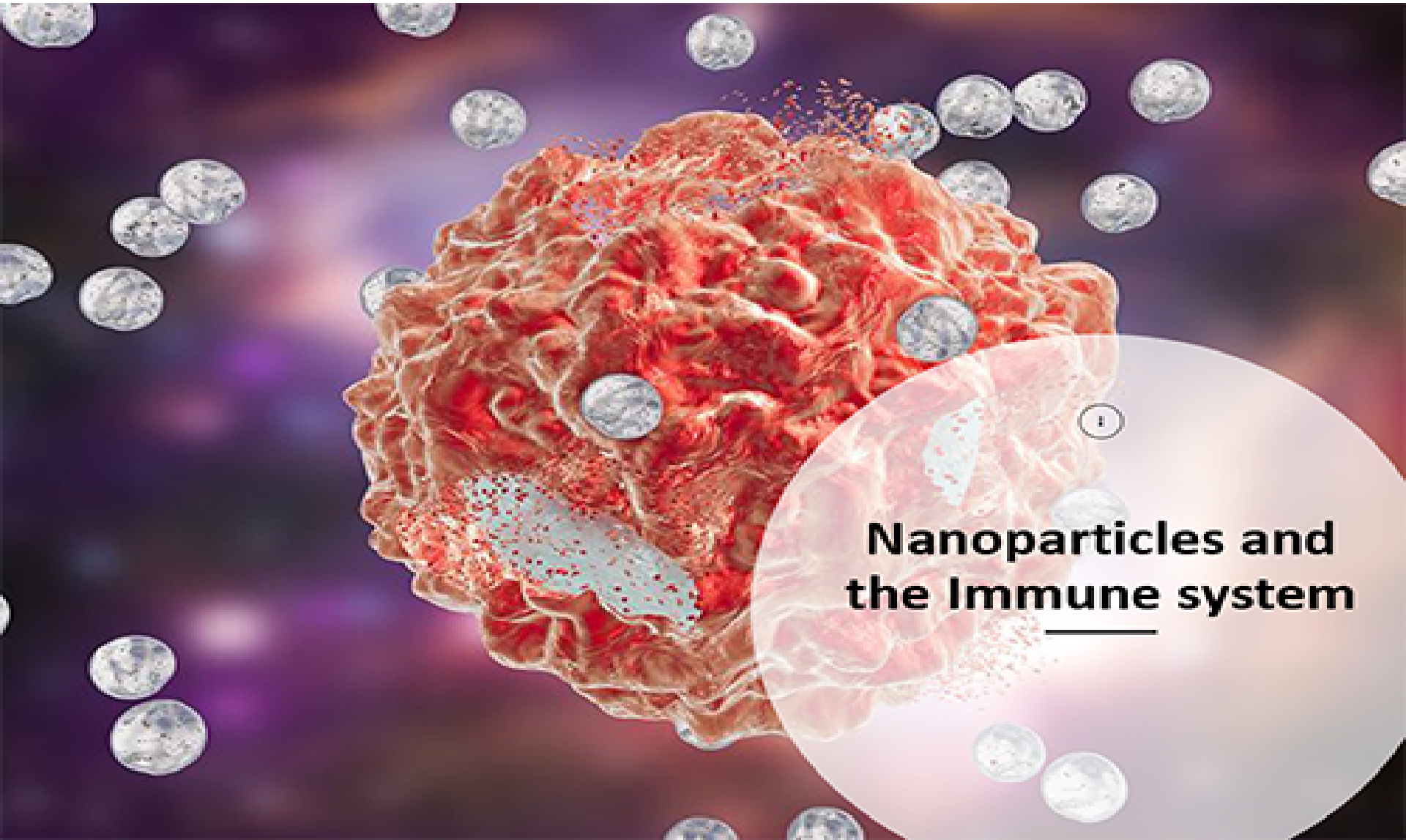
Toxicity

Concerns: Toxicity



- Both nanocarrier and API can be toxic
- API toxicity can "relocate" depending on the particle biodistribution

Nanoparticles



Terminology

Some terminology

- ***The innate immune system recognizes microbial products that are often essential for survival of the microbes (PAMPs)***

- ***The innate immune system also recognizes endogenous molecules that are produced by or released from damaged and dying cells***. These substances are called **damage-associated molecular patterns (DAMPs)**

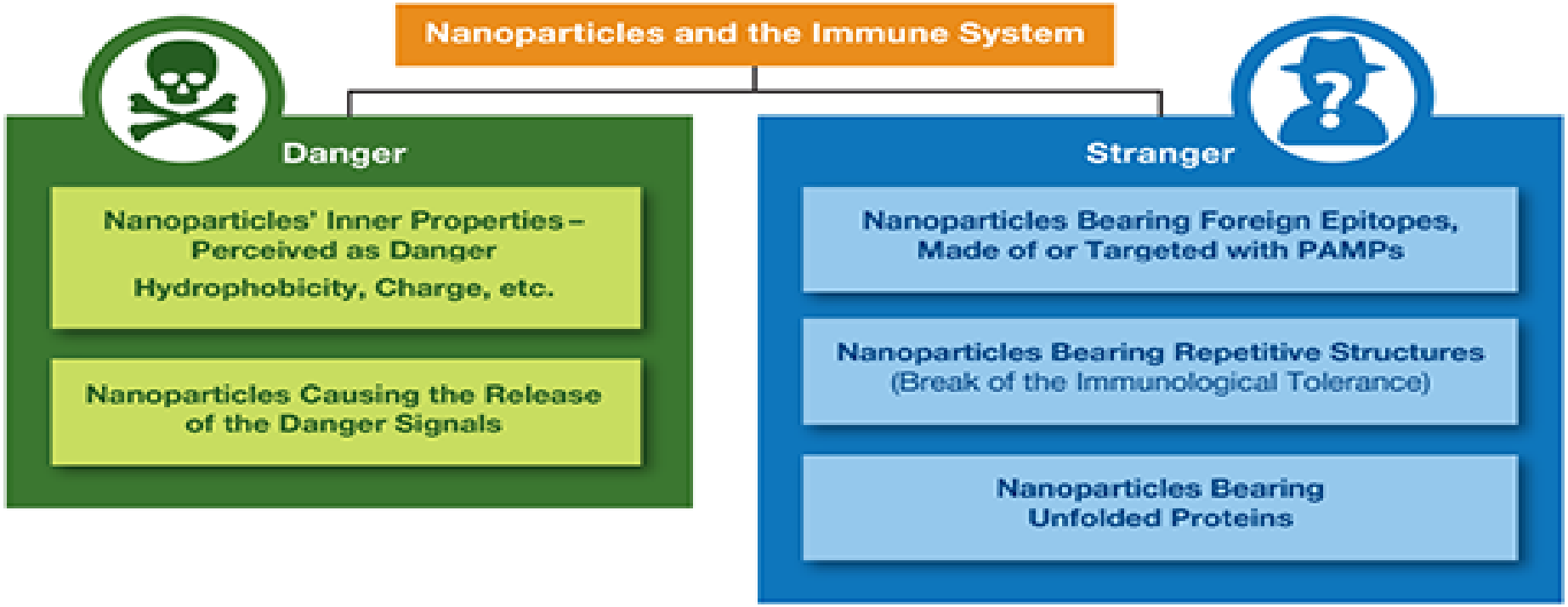
- ***The innate immune system uses several types of cellular receptors, present in different locations in cells, and soluble molecules in the blood and mucosal secretions, to recognize PAMPs and DAMPs***

NAMPs= Nanoparticle Associated Molecular Pattern

LAMPs= Life-style Associated Molecular Pattern

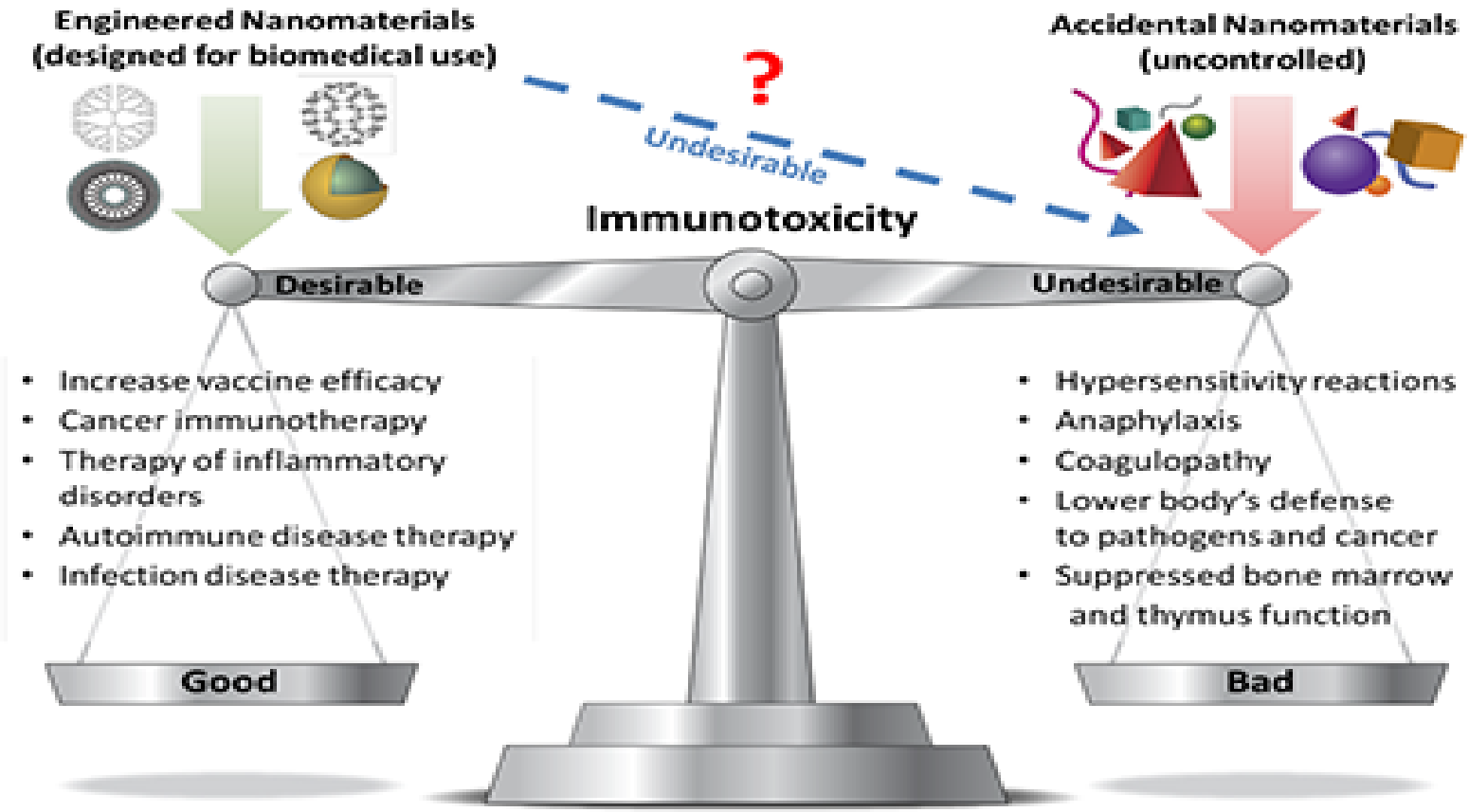
Immune system

Nanoparticles and the immune system



Nanoparticles

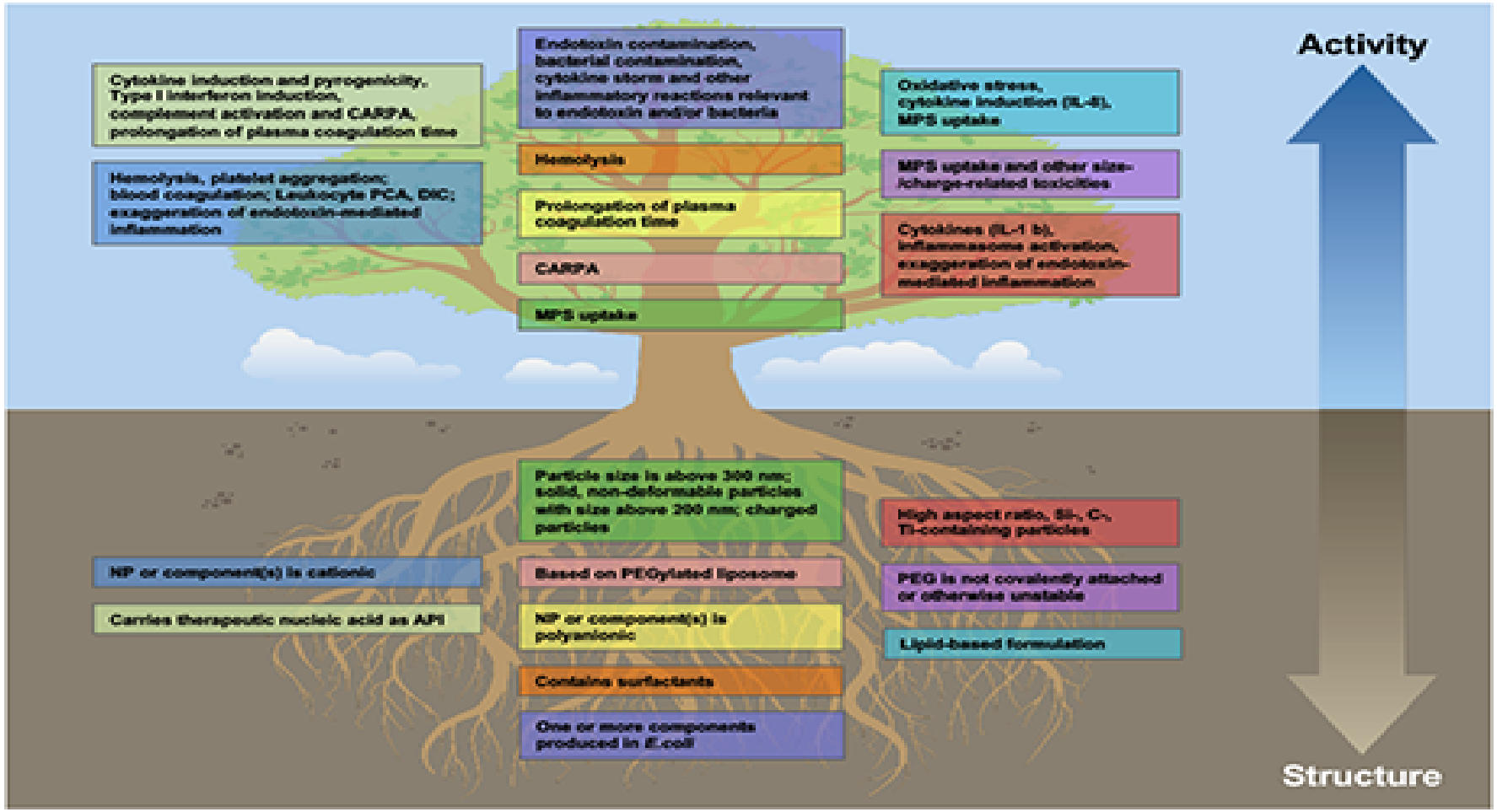
Nanoparticles and the immune system



Dobrovolskaia M.A.&McNeil. Handbook of immunological properties of engineered nanomaterials. WSP, 20012 ISBN 978-981-4390-25-5.

Structure activity relationship

Structure Activity Relationship



Immune system

Nanoparticles and the immune system

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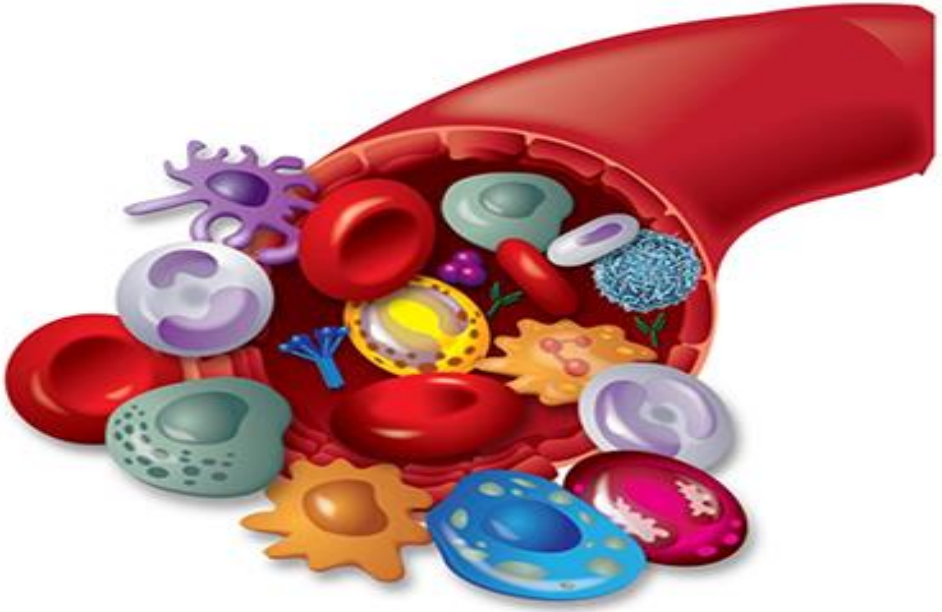
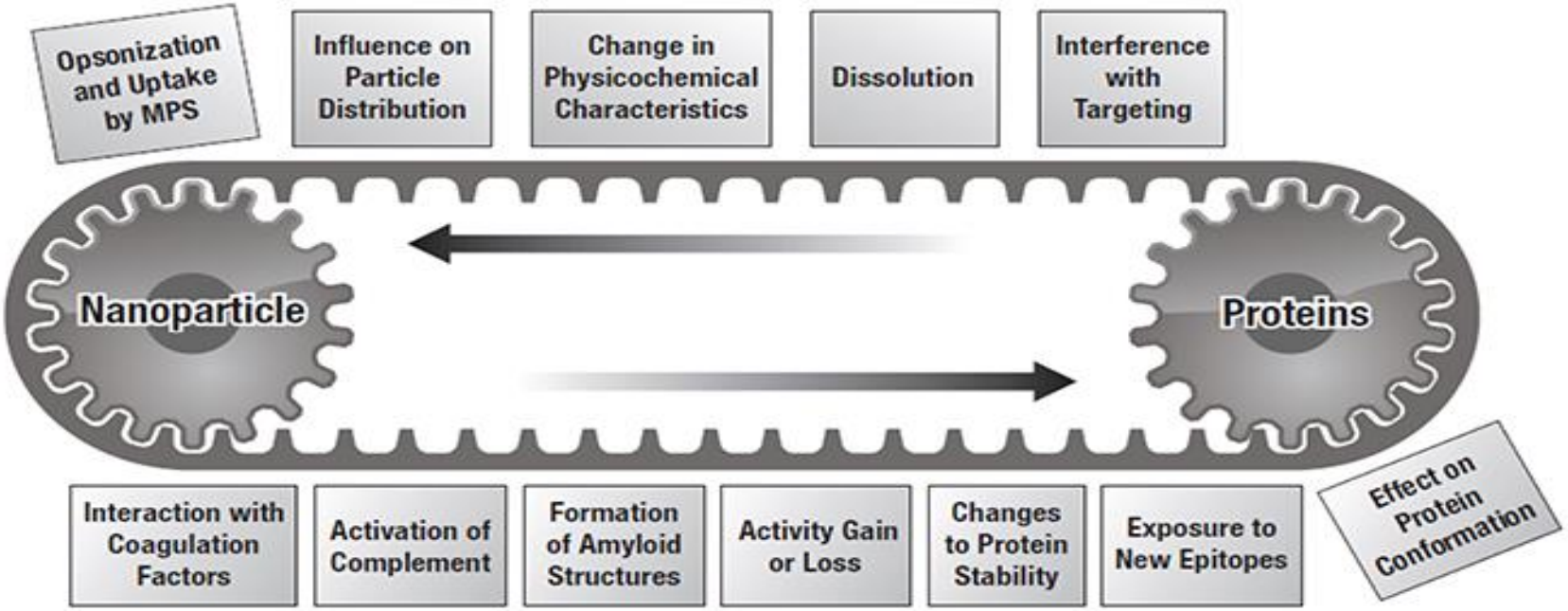
- Plasma Proteins
  - Biodistribution and MPS uptake
- Effects on erythrocytes
- Blood coagulation system
  - Platelets
  - Leukocytes
  - Endothelial cells
- Allergy
  - Complement activation
  - DTH
- Cytokines
- Immunogenicity



Bidirectional communication

Bidirectional Communication between Nanoparticles and Proteins



Binding of proteins to nanoparticle surface result in changes in particle properties
Properties and function of some proteins may also change after binding to the nanoparticle

Particle size

Particle size influences protein binding

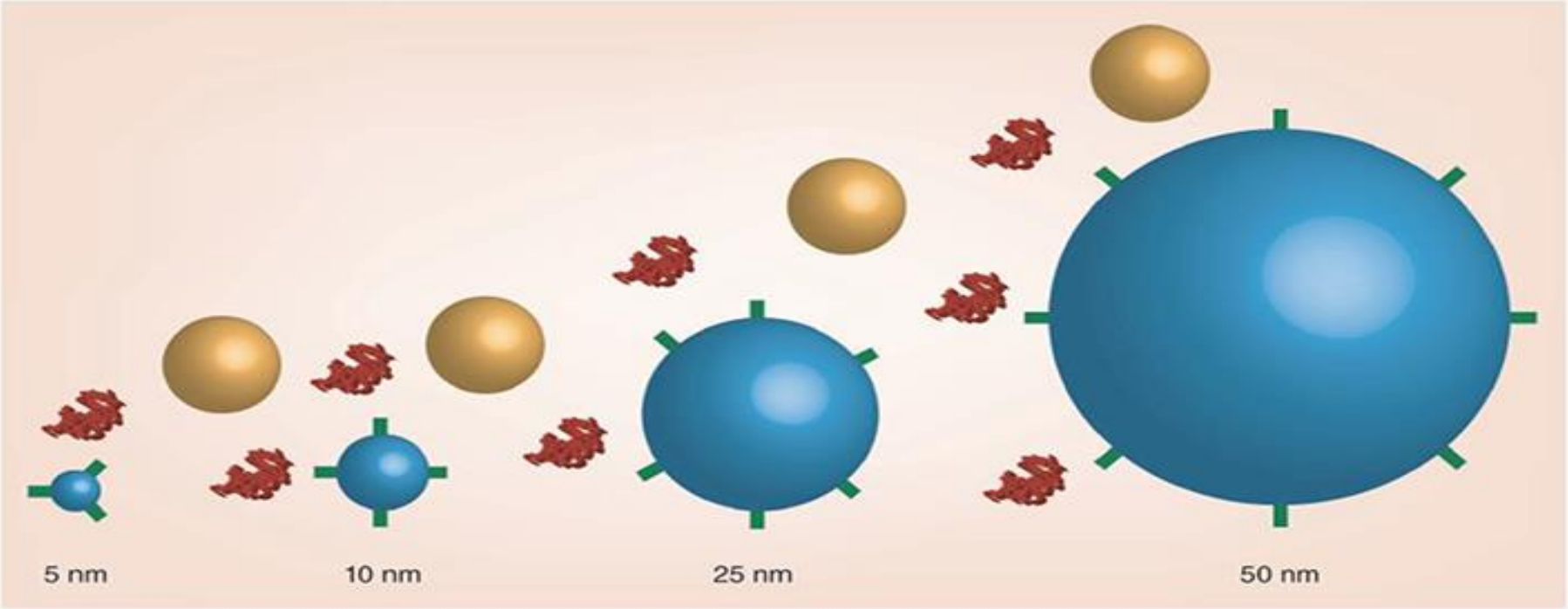


Figure 2. Size of proteins in the corona compared to nanoparticles of varying diameter. Nanoparticles are represented in blue and the diameter is given by the number under each particle in nm. Serum albumin[31] is shown in red and scaled relative to the nanoparticles. High-density lipoprotein is represented by orange spheres at a size of 12.5 nm diameter.

Cedervall Tet al, 2016. Handbook of Immunological properties of engineered nanomaterials

Protein binding

Protein binding affects particle size

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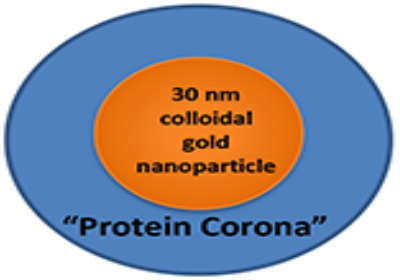
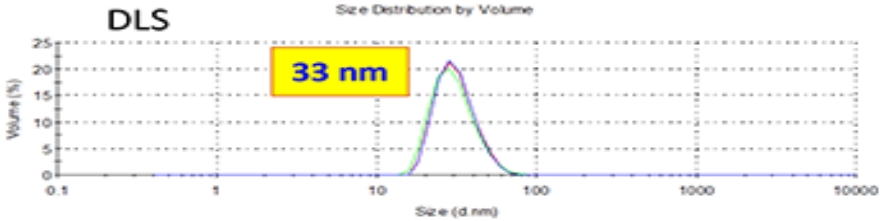
BEFORE

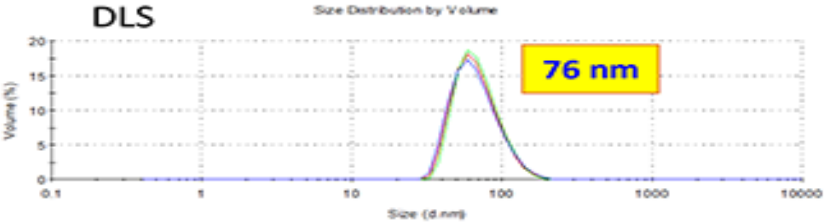
AFTER



DLS



DLS

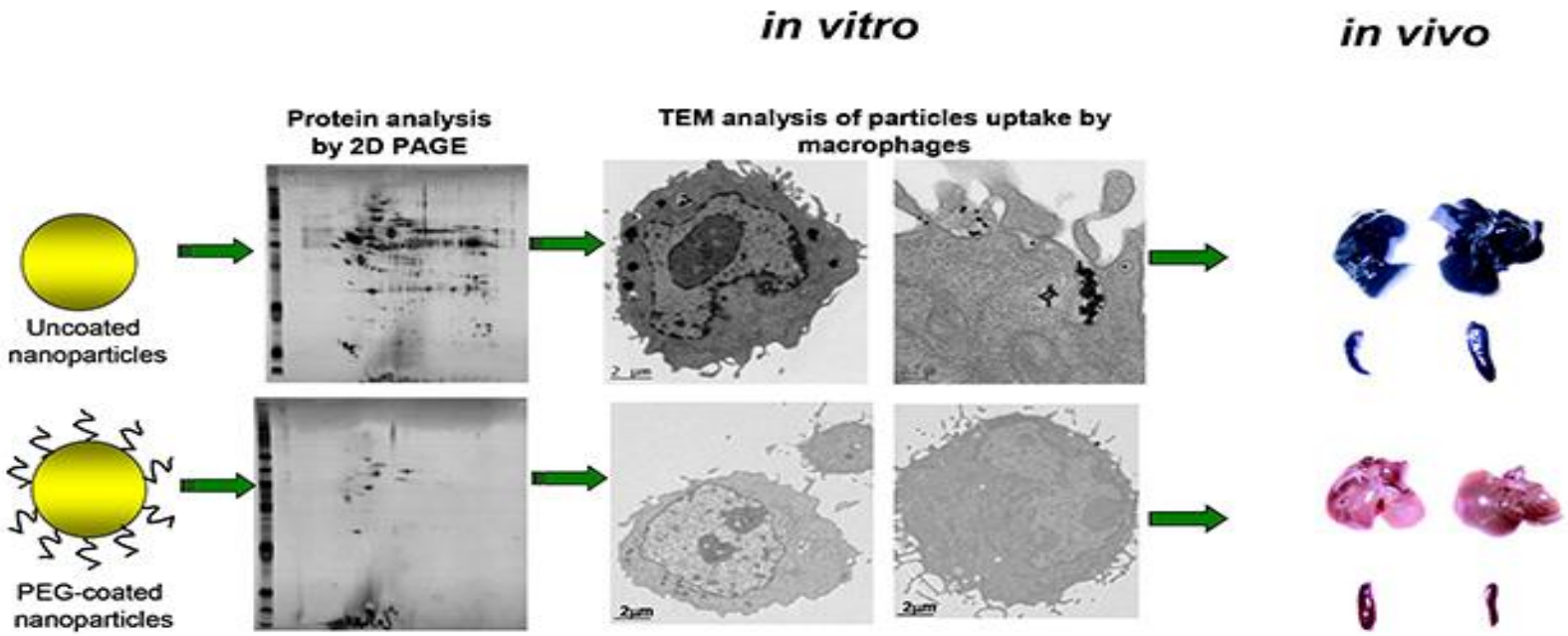


Incubation with human plasma increases hydrodynamic size of nanoparticles

Dobrovolskaia et al, (2009), Nanomed. Nanotechnol. Biol. Med., 5:106-117.

Biodistribution

Protein Binding and biodistribution



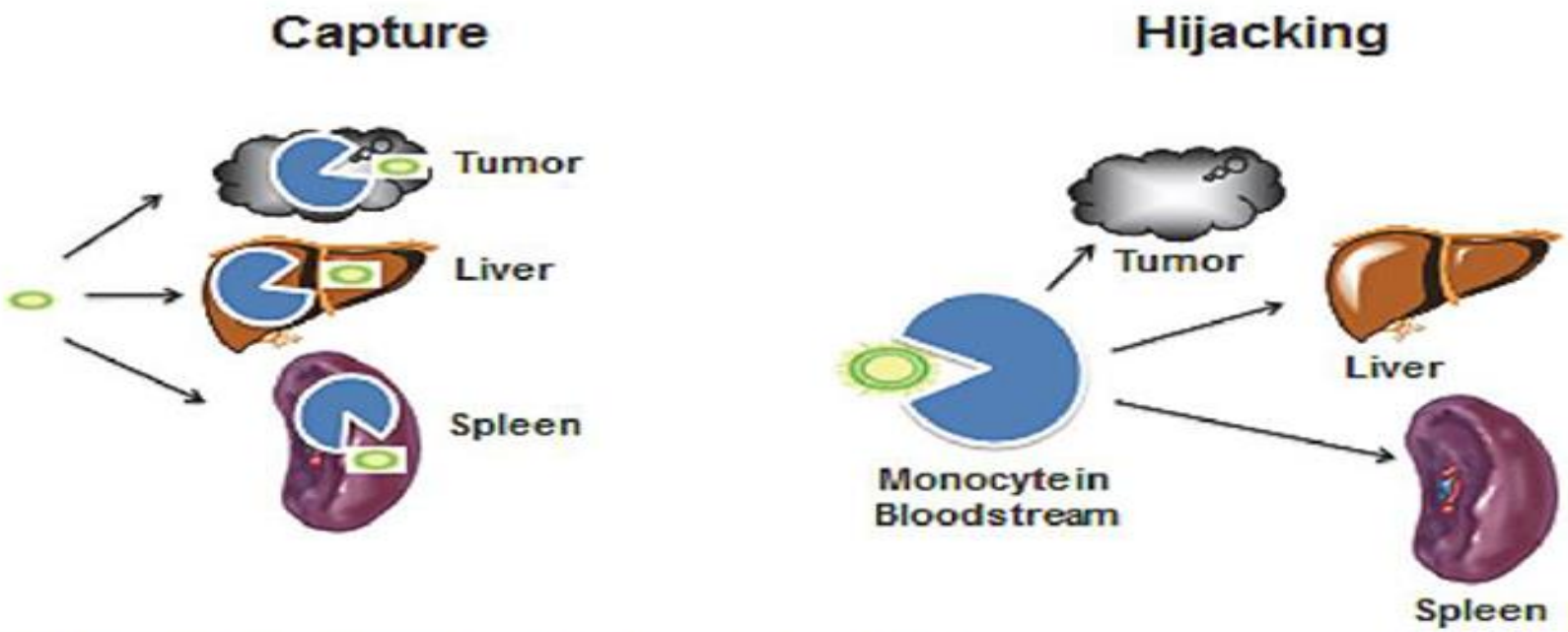
Dobrovolskaia et al., (2008), Mol.Pharm., 5:487-495.

Paciotti J. et al.,(2004), Drug Delivery,11:169-183.

- Particles which bind proteins are eliminated by MPS
- Particle surface protection (e.g with PEG) reduces protein binding and MPS
- Good correlation between in vitro and in vivo

MPS uptake

MPS uptake



- Two theories about nanoparticle distribution to the MPS
- Capture – uptake by phagocytic cells in the tissue
- Hijacking – uptake by circulating phagocytic cells which then take the particle to tissue

Zamboni et al, Handbook of Immunological properties of engineered nanomaterials(2016). V3

Macrophage polarization

Nanoparticles Influence Macrophage Polarization

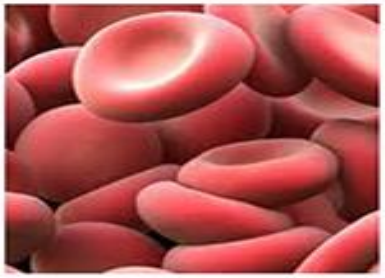
- Macrophages can acquire distinct functional capabilities depending on the types of activating stimuli they are exposed to
  - Classical M1 macrophages (efficient at killing microbes)
  - Alternative activation M2 macrophages (efficient at tissue remodeling and repair)

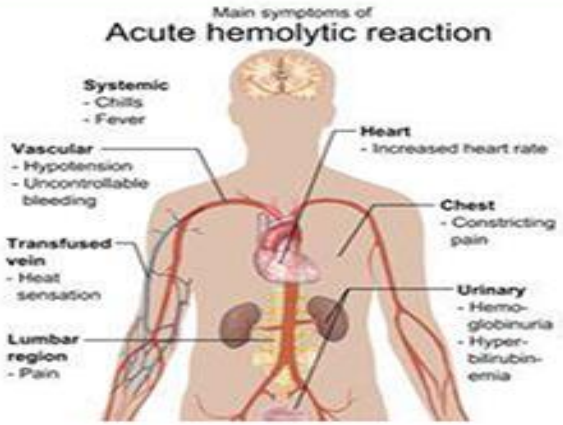
			M1 Markers				M2 Markers				
Nanoparticle Type	Overall Polarization Effect	Size Range (nm)	CD68/CD80/ CD86	IL-1β/IL-6/IL-12/ IL-23/TNF-α	iNOS/NO	ROS Generation	CD163/ CD206	IL-10	TGF-β	Arginase-1	Reference
Silica	M1-Like	10-1000	No Change	Increase	Increase	Increase	-	No Change	Increase	-	[59-64]
Gold	M1-Like	10-300	No Change	Increase	Increase	Increase	-	Decrease	-	-	[60, 70-73]
Polymeric	M2-Like	30-600	Decrease	Decrease	Decrease	Decrease	Increase	Increase	Decrease	Increase	[77-80]
Cationic Polymer	M1-Like	110-22000	Increase	Increase	Increase	Increase	Decrease	Decrease	Decrease	Increase	[85-93]
Liposome	M2-Like	70-400	-	Decrease	No Change	No Change	Increase	Increase	-	Increase	[96, 98, 99]
Carbon	M1-Like	70-70000	Increase	Increase	Increase	Decrease	Increase	Increase	No Change	Increase	[104-111]
Metallic	M1-Like	20-200	Increase	Increase	Increase	Increase	Decrease	Increase	-	Increase	[126-129, 136, 137, 139, 140]
Iron Oxide	M1-Like	30-200	Increase	Increase	Increase	Increase	Decrease	Increase	-	Decrease	[150, 151, 154, 155, 161, 162, 165, 174]

Reichel D et al., 2019; 3(1): 66-88. doi: 10.7150/ntoo.30052

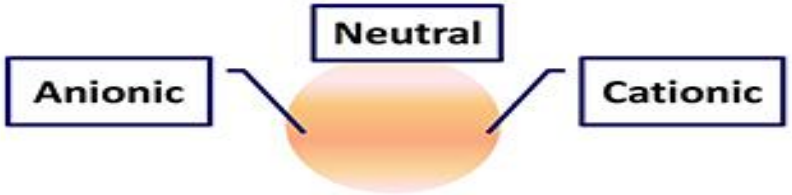
Hemolysis

Hemolysis





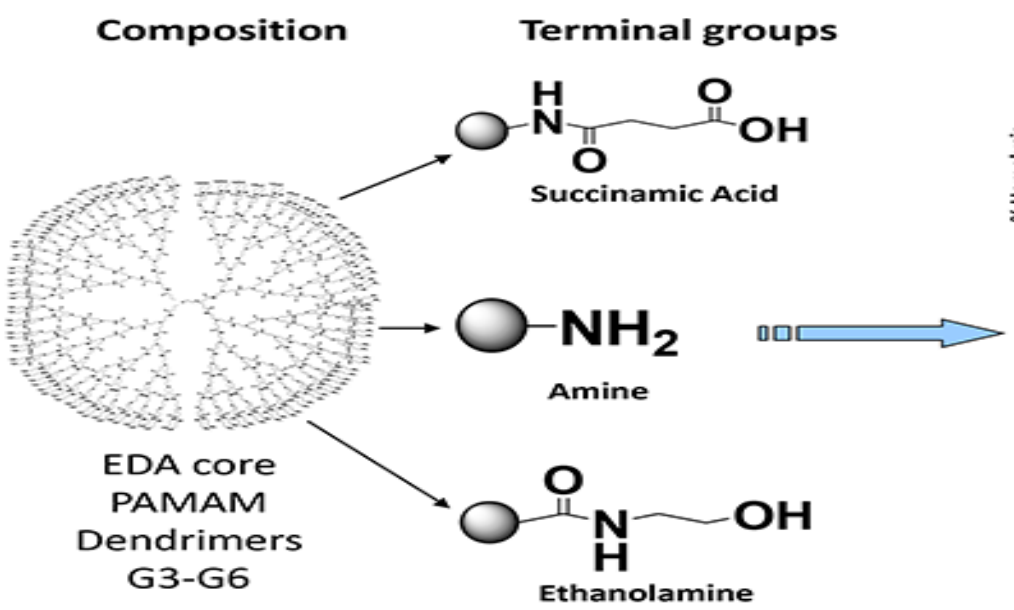
Role of Nanoparticle Size

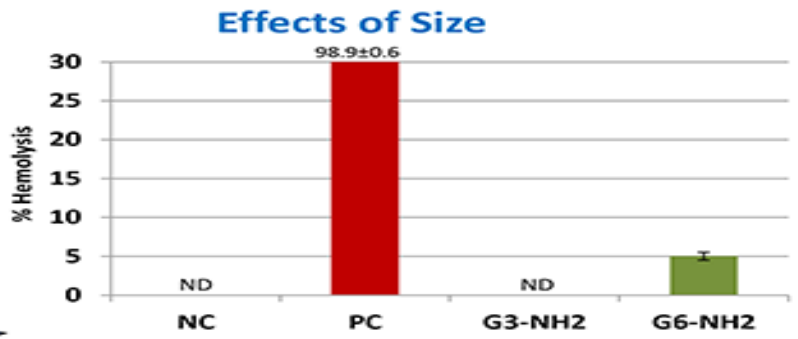


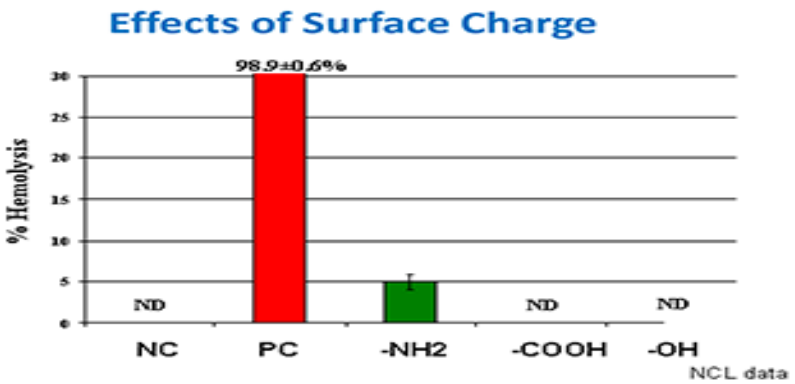
Role of Nanoparticle Surface Charge

Hemolysis

Hemolysis







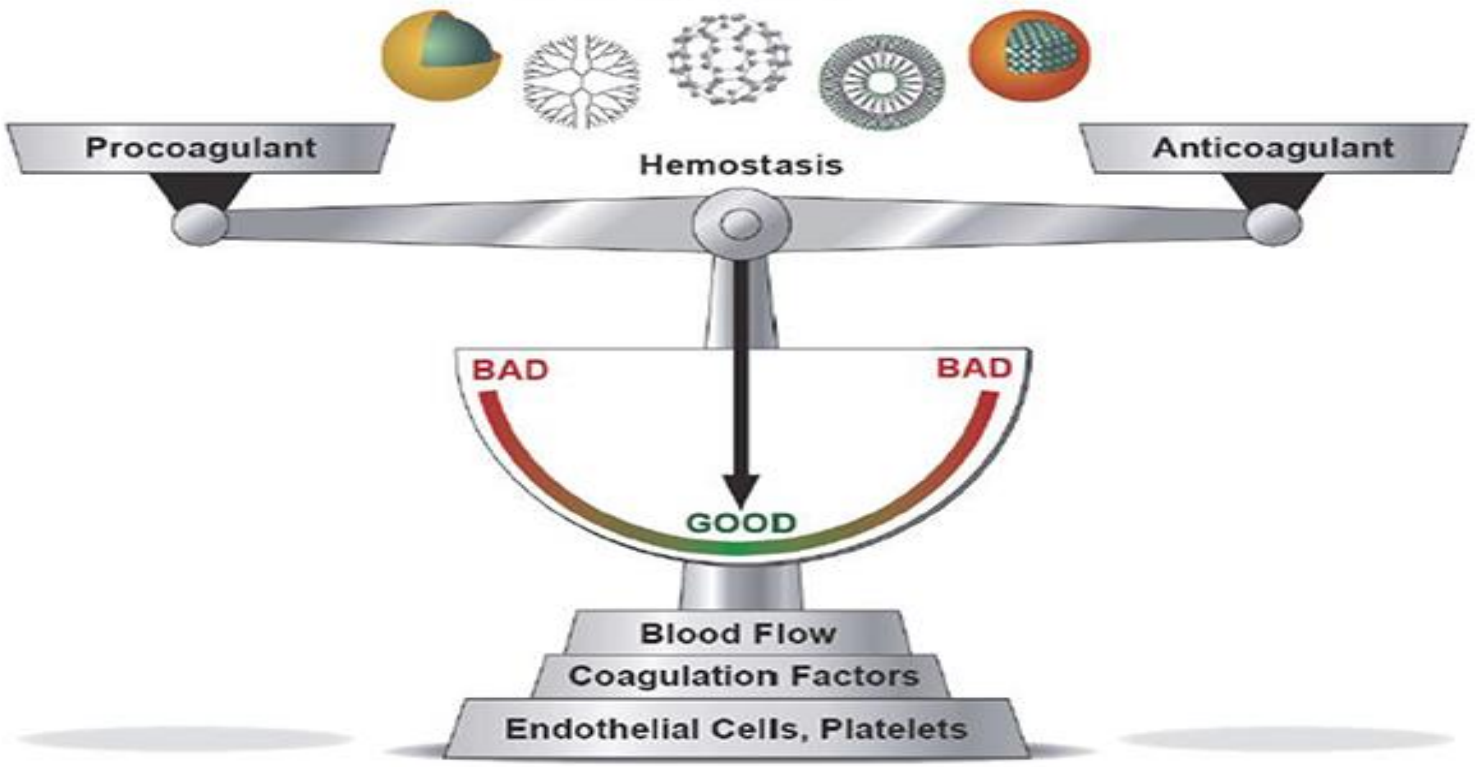
- Cationic dendrimers are more hemolytic than their anionic and neutral counterparts of the same size
- Larger dendrimers are more hemolytic than smaller

NC = negative control;; PC = positive control; EDA = ethylenediamine; PAMAM = poly(amidoamine)

Coagulation system

Coagulation system

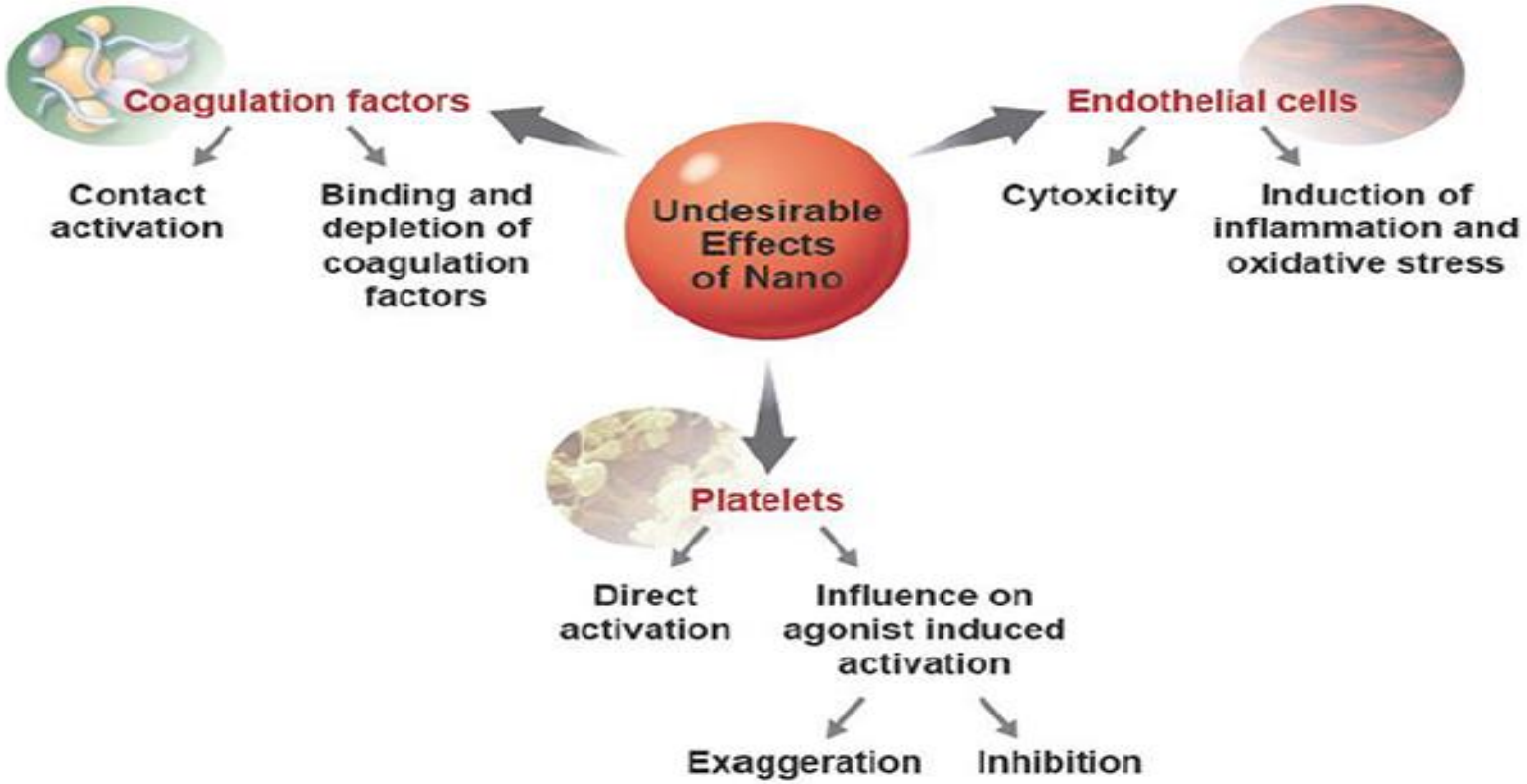
Nanoparticles can be engineered to avoid or specifically interact with coagulation system.



Ilinskaya A& Dobrovolskaia MA. Handbook of Immunological properties of Engineered Nanomaterials (2016), Vol 2

Undesirable effects

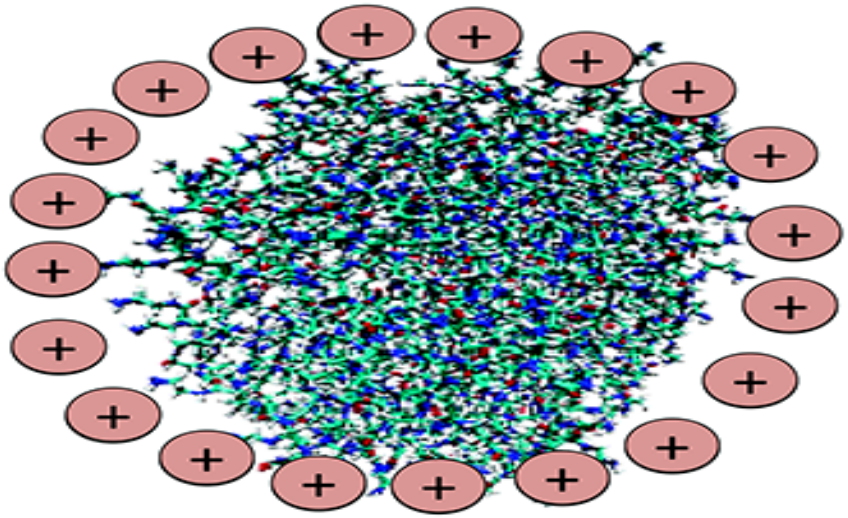
Undesirbale effects on coagulation

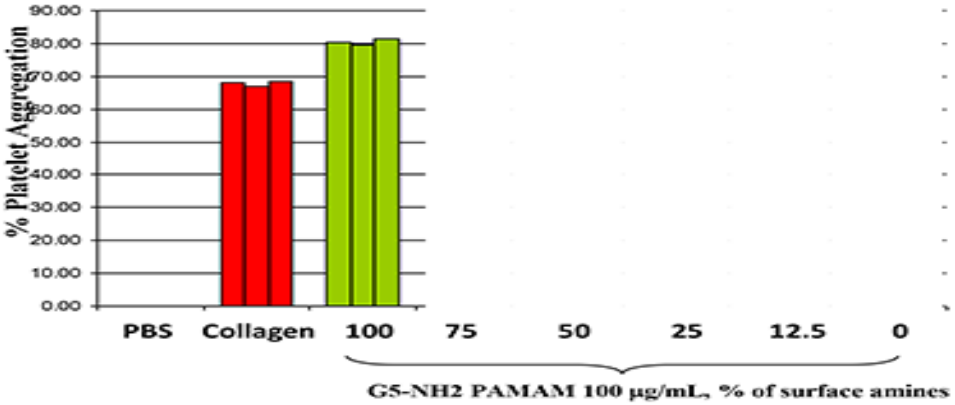


Ilinskaya A& Dobrovolskaia MA. Handbook of Immunological properties of Engineered Nanomaterials (2016), Vol 2

Zeta potential

Platelets: role of zeta potential

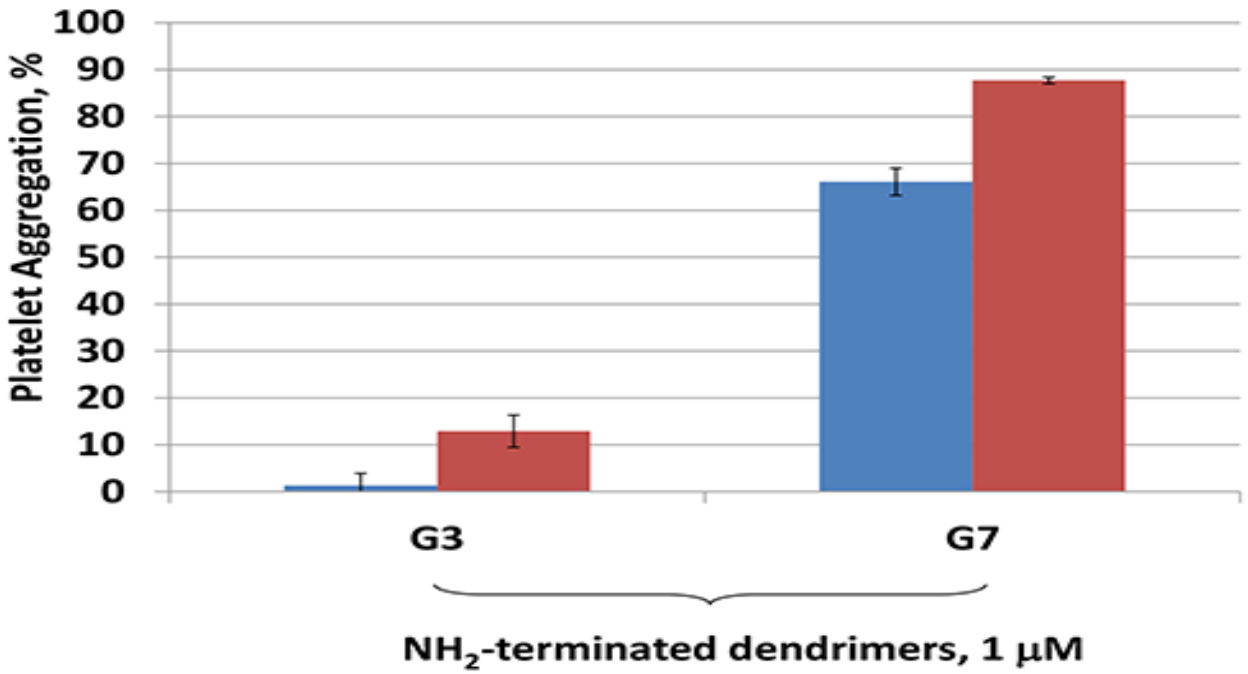


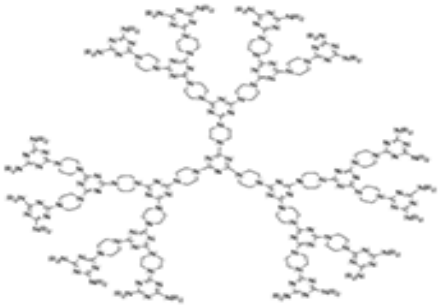


Zeta Potential is important
Less surface amines = less platelet aggregation

Platelets

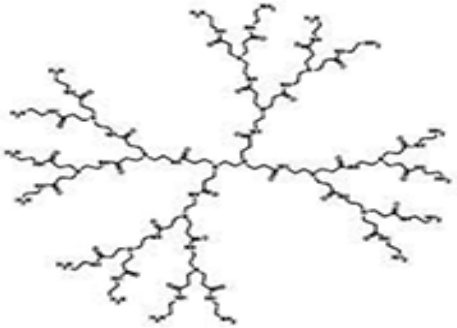
Platelets: effect of composition





Triazine

PAMAM

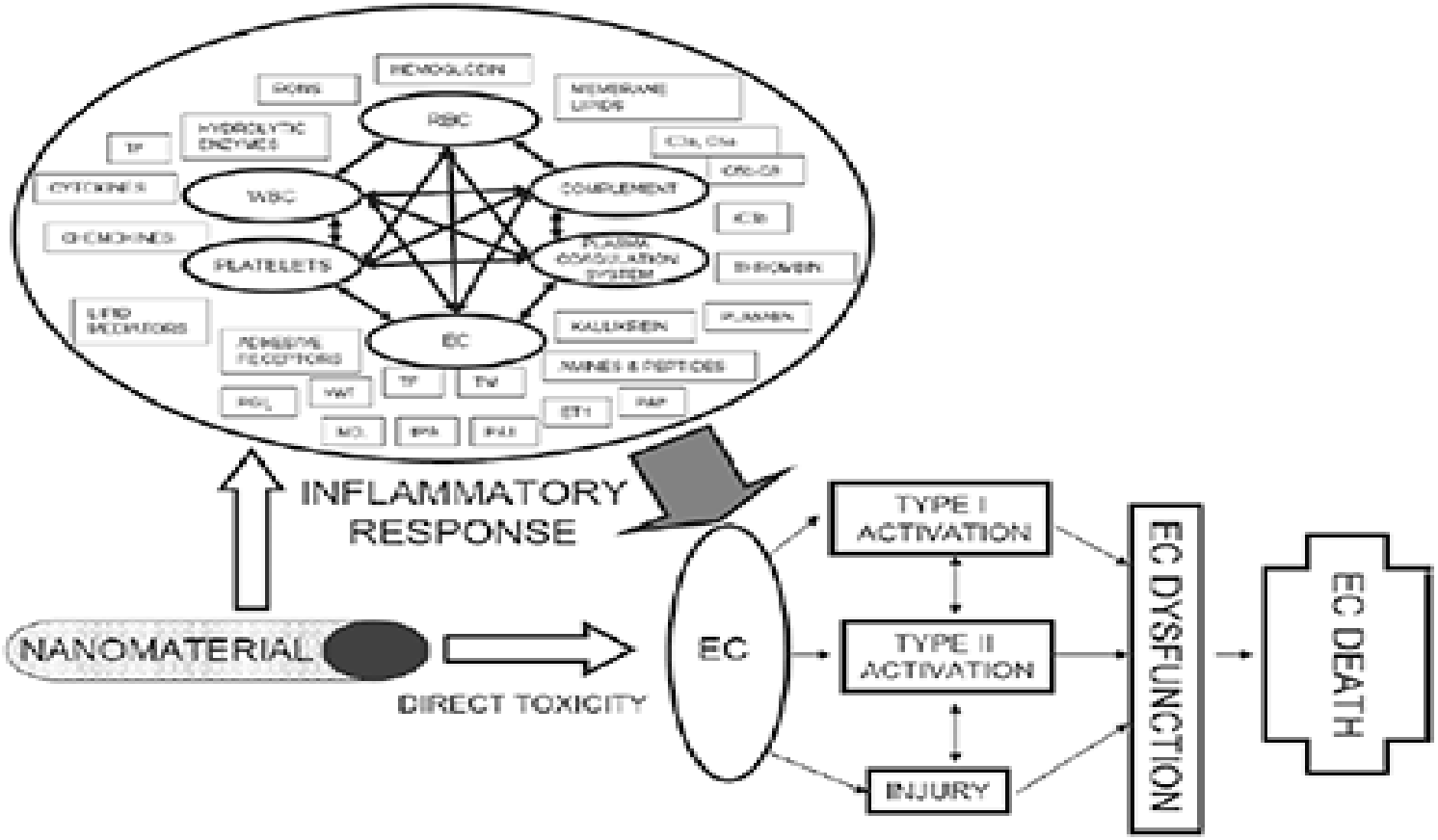


Triazine dendrimers are less potent in inducing platelet aggregation than their PAMAM counterparts

Triazine dendrimers were kindly provided by Dr.Eric Simanek, Texas Christian University

Endothelial cells

Effects on endothelial cells



Simak J. Handbook of Immunological properties of Engineered Nanomaterials (2016), Vol 2

Complement activation

Complement activation

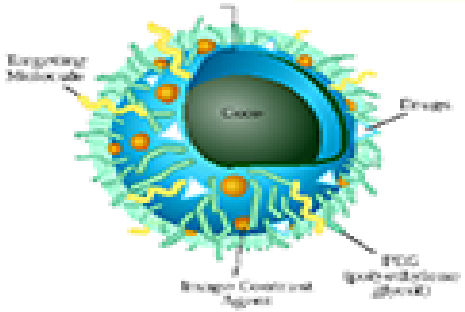
Complement

Nonspecific clearance of pathogens

- Hypersensitivity reactions
- Anaphylaxis

- Enhances B-cell responses to antigen
- Promotes T-cell activation
- Promotes DC activation

- Humoral immune response
- Cellular immune response



Nanotechnology-based pharmaceuticals

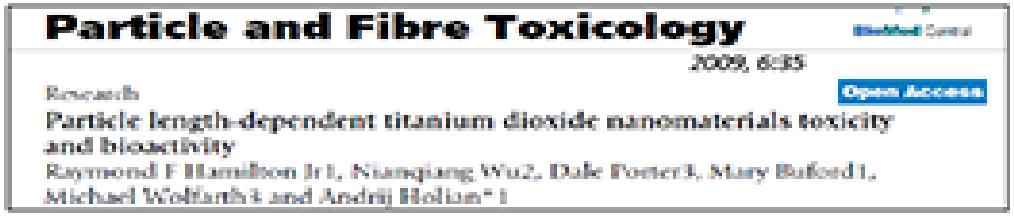
If particles are intended for systemic administration complement activation should be avoided

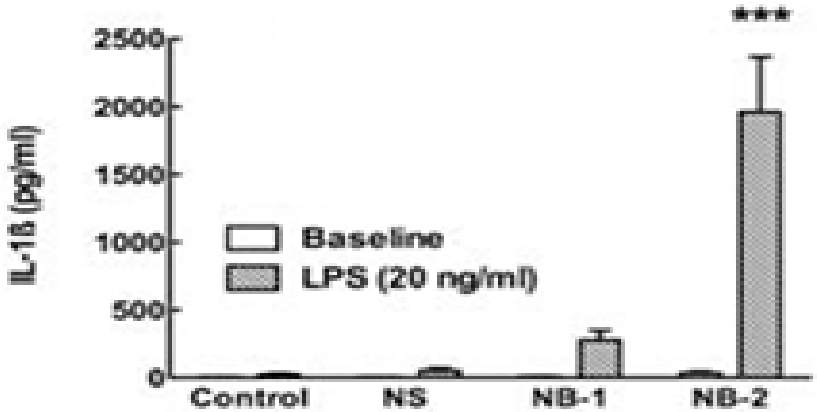
If particles are intended for s.c. & i.d. routes, complement activation may benefit vaccine efficacy

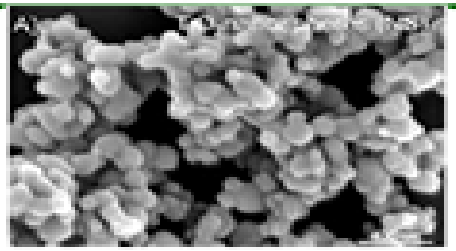
DC = dendritic cell; s.c. = subcutaneous; i.d. = intradermal

Fibrous carriers

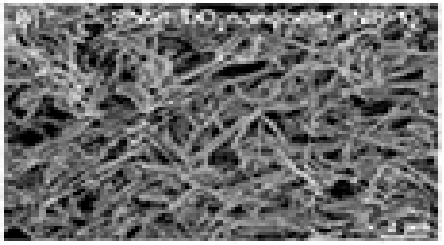
Fibrous Carriers induce IL-1


Particle and Fibre Toxicology
2009, 6:35
Open Access
Research
Particle length-dependent titanium dioxide nanomaterials toxicity and bioactivity
Raymond F Hamilton Jr1, Nianqiang Wu2, Dale Porter3, Mary Buford1, Michael Wolfarth3 and Andrij Holian*1

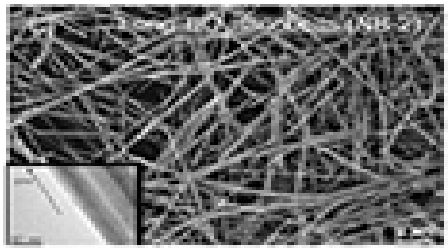




TiO_2 Nanospheres (NS)



TiO_2 Short Nanobelts (NB-1)



TiO_2 Long Nanobelts (NB-2)

- **Long fibrous TiO_2 nanoparticles enhanced endotoxin-mediated IL-1**
- **Cationic dendrimers have similar property**
- **Enhancement of endotoxin-mediated inflammation is a serious safety concern due to common contamination of nanomaterials with bacterial LPS**

IL-1 induction

Mechanism of IL-1 induction

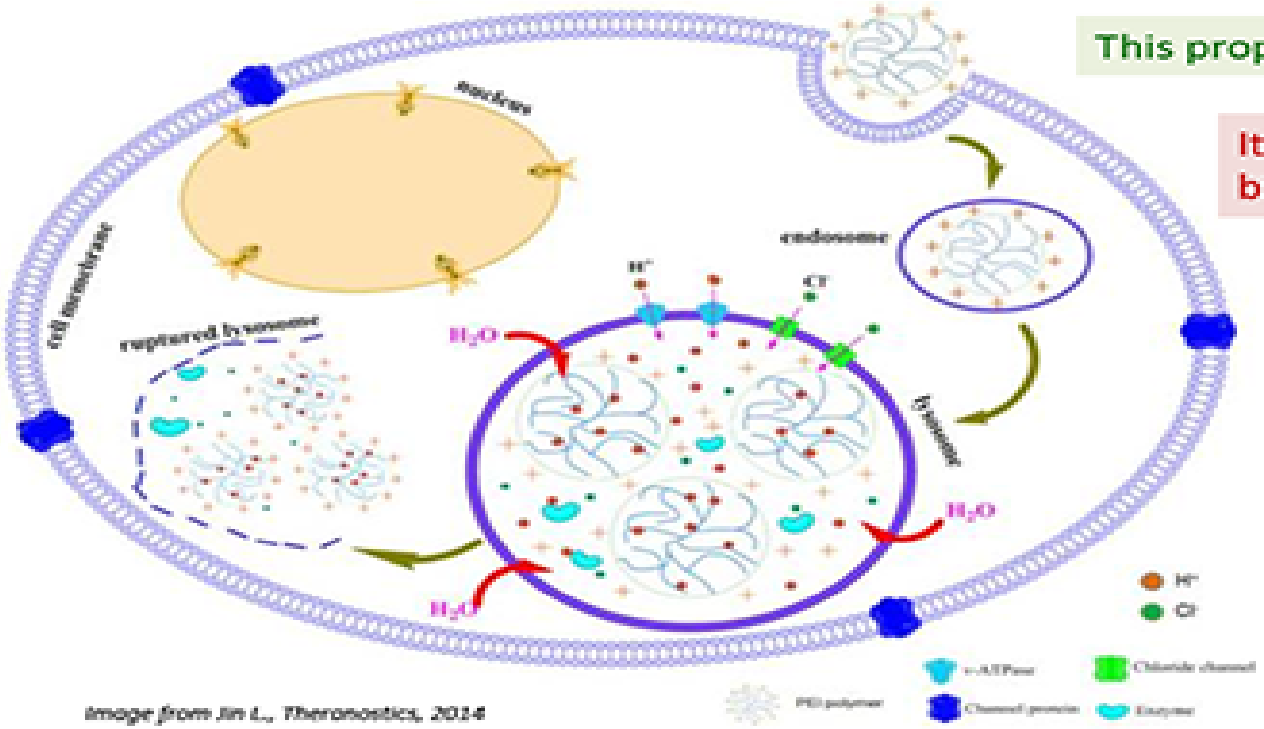


Image from Jin L., Theranostics, 2014

This property is beneficial for vaccines

It creates safety concerns for biotechnology therapeutics

Fibrous and Cationic particles induce IL-1β through activation of NLRP3 inflammasome triggered by a proton-sponge mechanism

Cationic liposomes

Cationic Liposomes induce broad spectrum of cytokines

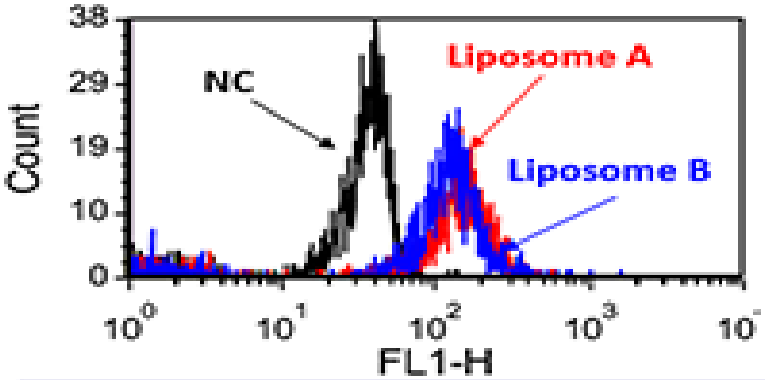
Cationic Liposomes

	IFN-γ	IL-1α	IL-1β	IL-6	IL-8	IL-10	MCP-1	MIP-1α	MIP-1β	RANTES	TNF-α
donor #1	-	++	++	+++	+++	+	+++	+++	++	++	++
donor #2	-	++	++	+++	+++	+	+++	+++	++	++	++
donor #3	-	++	++	+++	+++	+	+++	+++	++	+++	++
donor #4	-	++	++	+++	+++	+	+	+	+	++	++
donor #5	-	++	++	+++	+++	+	++	++	++	++	++
donor #6	-	++	++	+++	+++	+	++	+++	++	++	++
donor #7	-	+	+	++	+++	+	++	+++	+	++	++

Detected cytokines	IL-1α	IL-1β	IL-6	TNF-α	IL-10	IL-8	MCP-1	MIP-1α	MIP-1β	RANTES
Group:	cytokines					chemokines				

Detected danger signals	MMP-1	MMP-7	MMP-9
Group:	metalloproteinases		

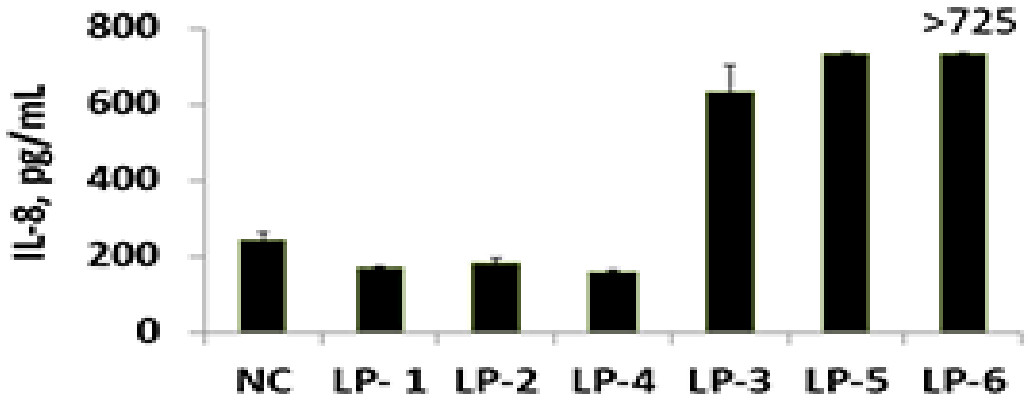
- Cationic liposomes induce wide range of pro-inflammatory responses
- While cytokines are needed for adjuvanticity, excessive secretion of some of them (e.g. TNFa) often leads to side effects (necrosis at the injection site)

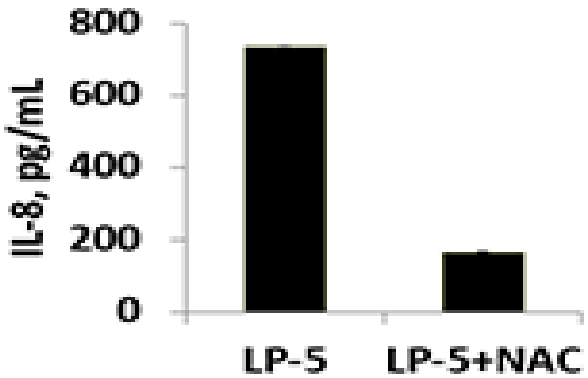


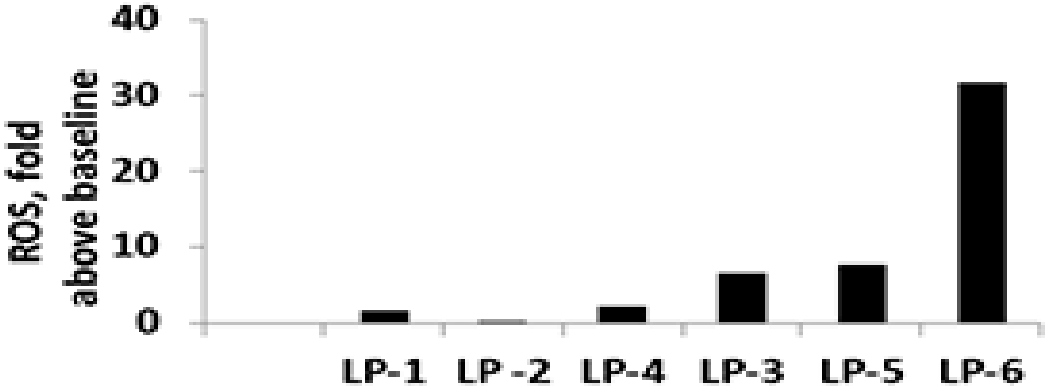
Oxidative stress is underlying mechanism

Chemokine induction

Anionic liposomes induce chemokines







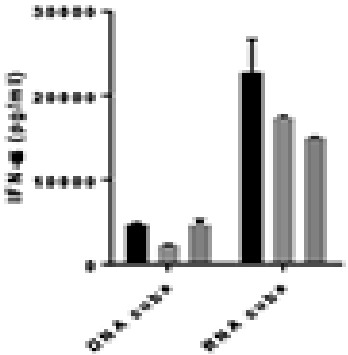
- Induction of IL-8 by liposomes follows induction of oxidative stress and can be prevented by antioxidant N-acetyl cysteine

IFN induction

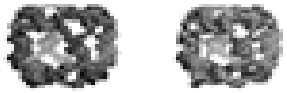
Nucleic Acid Nanoparticles induce IFN

These data are generated in collaboration with UNCC:
Dr. Kirill Afonin
Weina Ke
Justin Halman

Composition

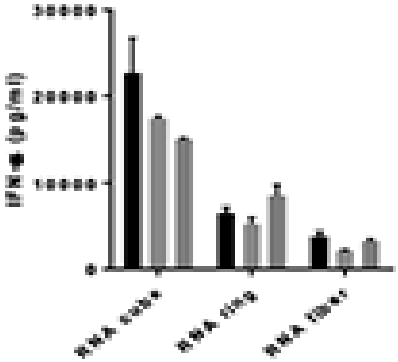


DNA < RNA



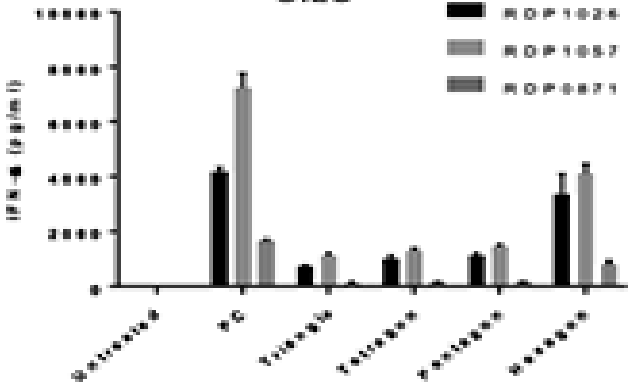
RNA nanoparticles are more potent than DNA nanoparticles

Architecture



Globular particles are more potent than planar than fibrous particles

Size



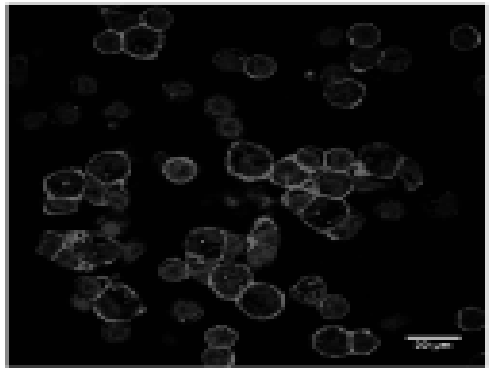
Larger particles are more potent their smaller particles

Hong E., et al., NanoLetters, 2018

IFN induction

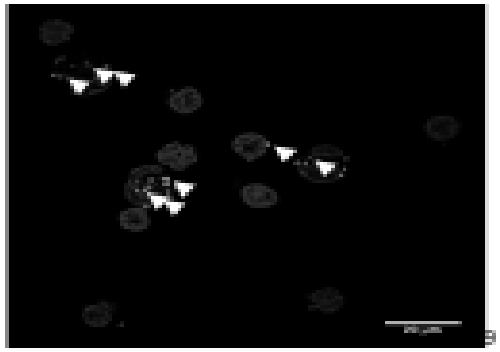
Mechanism of IFN induction

Internalization



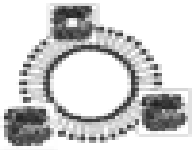
Red: Cell membrane (wheat germ agglutinin AF594)
Green: Nanoparticles (RNA cube, AF488)
Blue: Nucleus (DAPI)

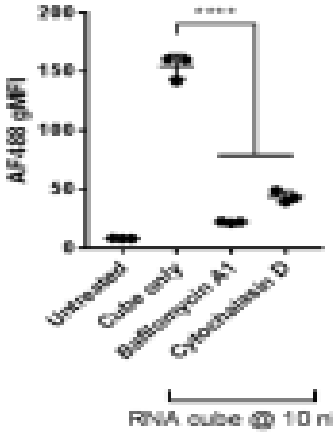
Co-localization with endolysosomal pathway

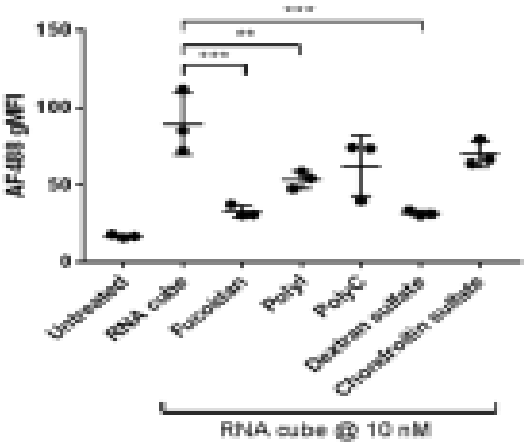


Red: Endolysosomes (Lyso-ID Red)
Green: Nanoparticles (RNA cube, AF488)
Blue: Nucleus (DAPI)

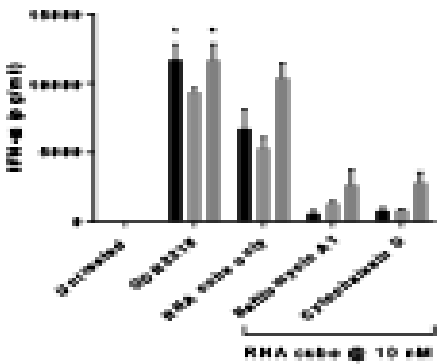
Inhibition of particles uptake by SR-mediated endocytosis....

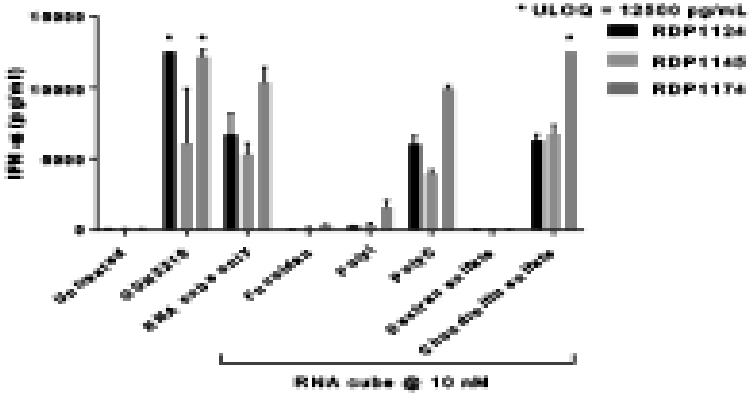






.... correlates with inhibition of IFN production

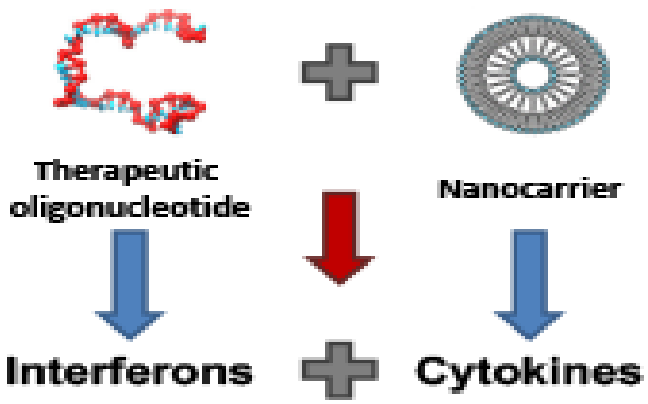


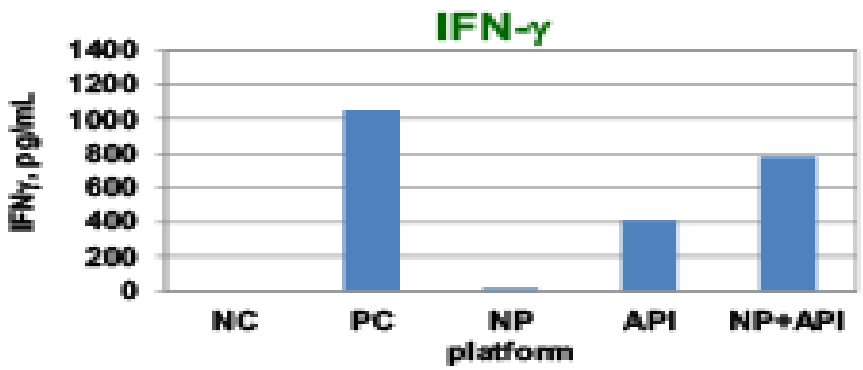


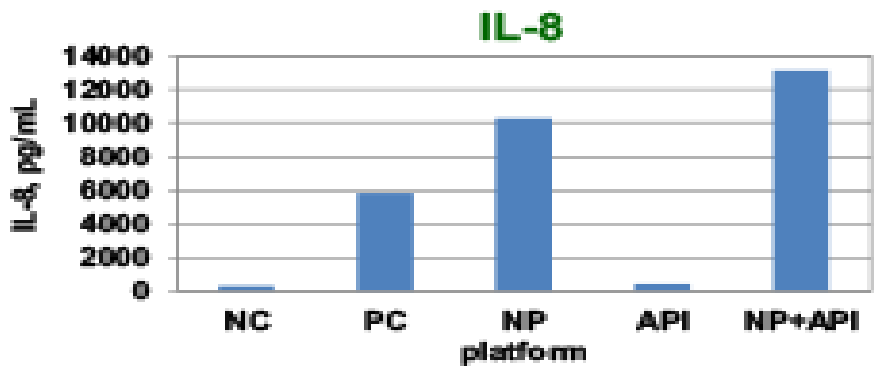
Hong E., et al., NanoLetters, 2018

API immunotoxicity

Carrier contribution to API immunotoxicity







Nanocarriers may contribute to immunostimulation profile of API

Platform selection

Considerations for platform selection

Desirable Properties

For Systemic Administration Non-immune Applications

- Inhibition of TLR Signaling
- Inhibition/Prevention of Complement Activation
- Inhibition/Prevention of Thrombogenicity
- Inhibition/Prevention of Cytokine Response
- No Effect or Inhibition of Endotoxin Signaling

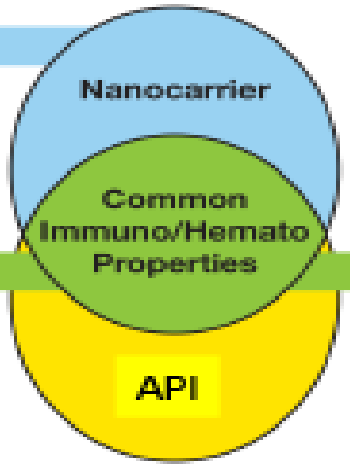
Examples:
PEGylated Gold Nanoparticles, Anionic Gold Nanoparticles, and Certain Polymers

Desirable Properties

For IMO, Vaccines and Other Applications Where Immuno-stimulation Is Desirable

- Complement Activation
- Cytokine Induction

Examples:
Lipid-Based Nanoparticles and Certain Polymers



Undesirable Properties

- Cytokine Induction
- Complement Activation
- Coagulopathy (DIC and DIC-like Reactions)
- Exaggeration of Endotoxin Responses

For Systemic Administration Non-immune Applications

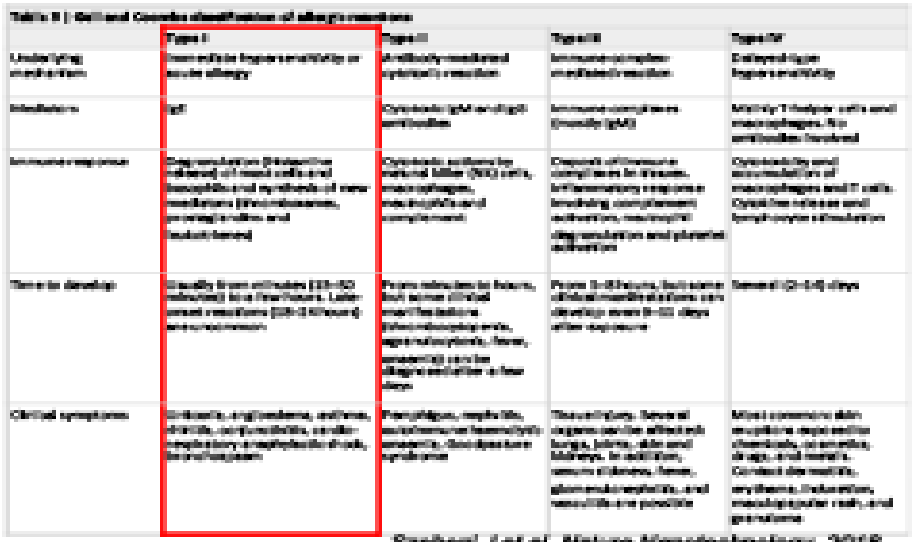
Examples:
Liposomes and Lipid-Based Nanoparticles, Cationic Polymers, and Cationic Dendrimers

- Immunotoxicity of both API and nanocarrier should be considered.
- Use immunologically reactive carrier when immunomodulation is wanted.
- Avoid such platforms when immunoreactivity is undesirable.

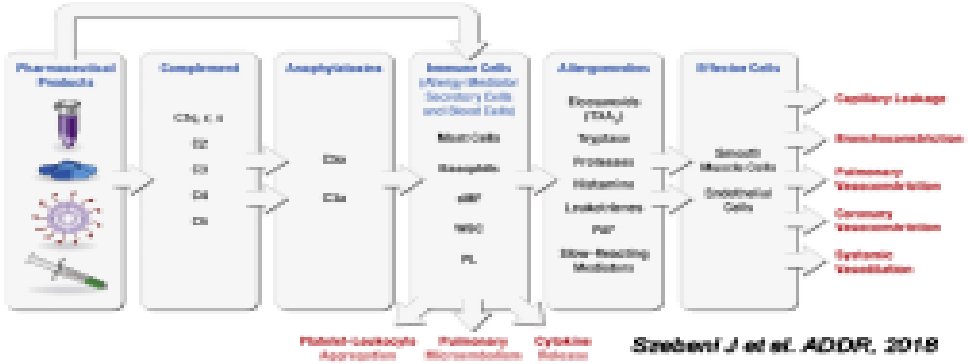
Dobrovolskaia MA& McNeil SE, EODD, 2015.

Infusion reactions

First Generation Liposomes & Infusion Reactions



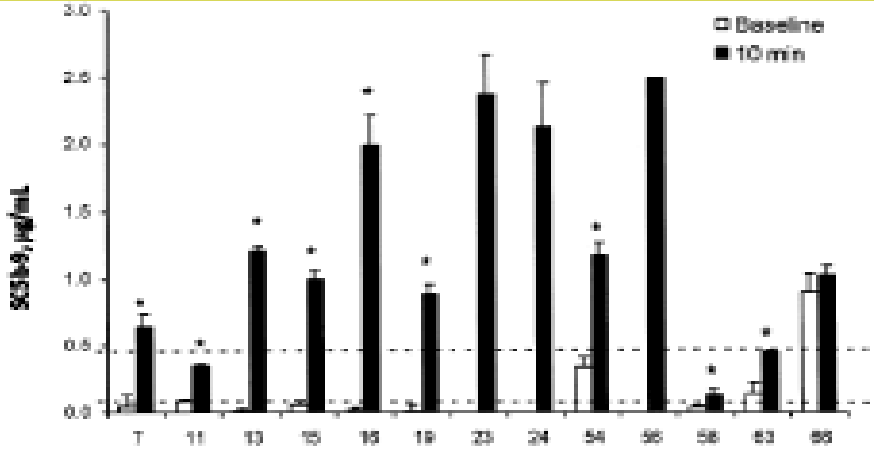
Szebeni J et al. Nature Nanotechnology, 2018



Szebeni J et al. ADDR, 2018

Activation of complement, and complement-dependent and –independent induction of cytokines underly IRs to liposomes

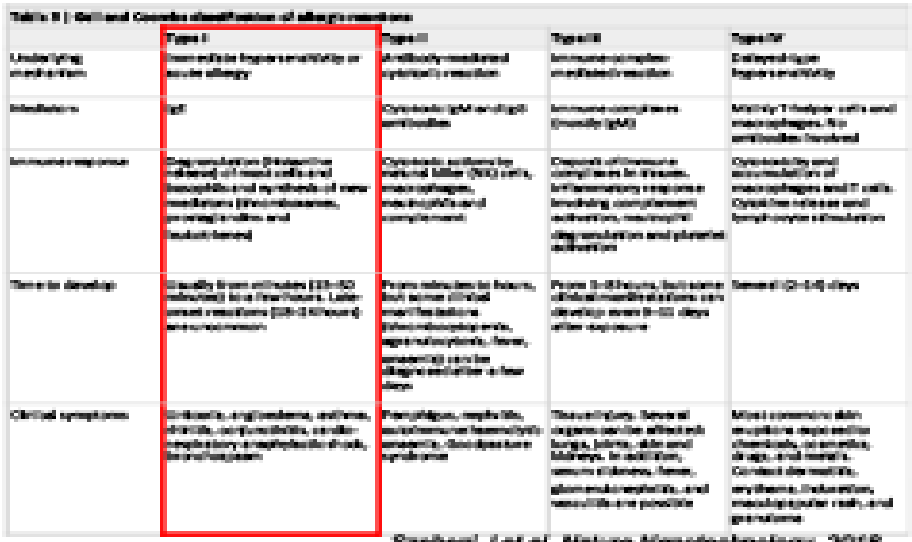
- Infusion reactions to PEGylated liposomes fit Gell and Coombs classification for Type I HR, but mediated by complement instead of IgE
- These IRs are often called anaphylactoid, pseudoallergy or CARPA



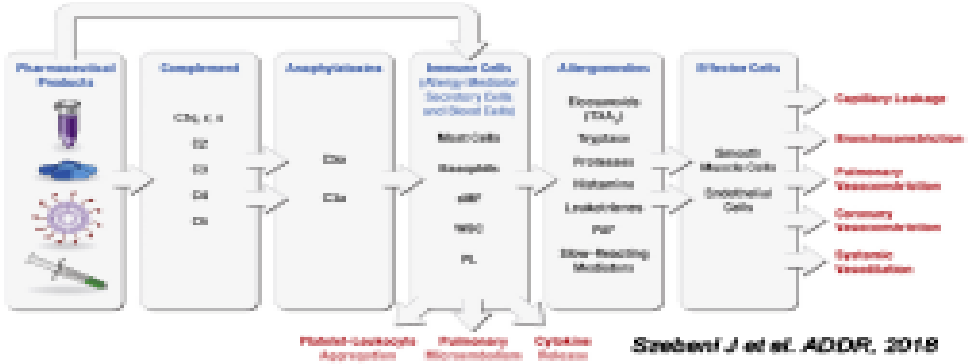
Chanan-Khan et al., (2003) Ann. Oncol., 14:1430-1437

Infusion reactions

First Generation Liposomes & Infusion Reactions



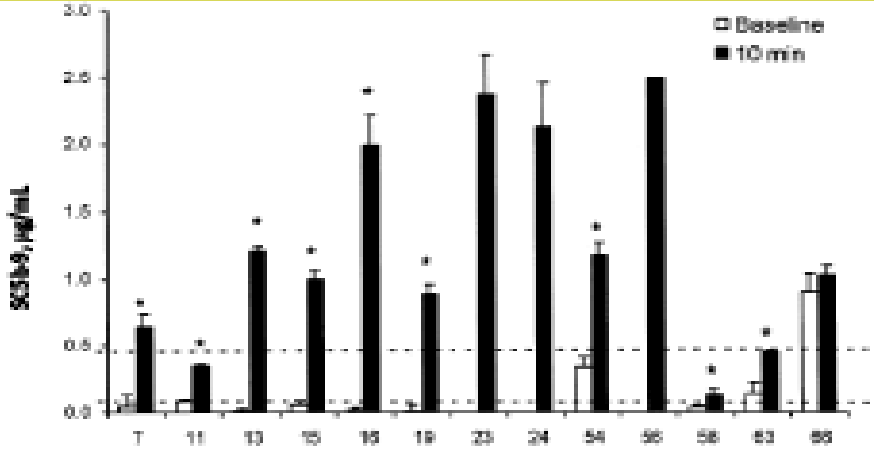
Szebeni J et al. Nature Nanotechnology, 2018



Szebeni J et al. ADDR, 2018

Activation of complement, and complement-dependent and –independent induction of cytokines underly IRs to liposomes

- Infusion reactions to PEGylated liposomes fit Gell and Coombs classification for Type I HR, but mediated by complement instead of IgE
- These IRs are often called anaphylactoid, pseudoallergy or CARPA



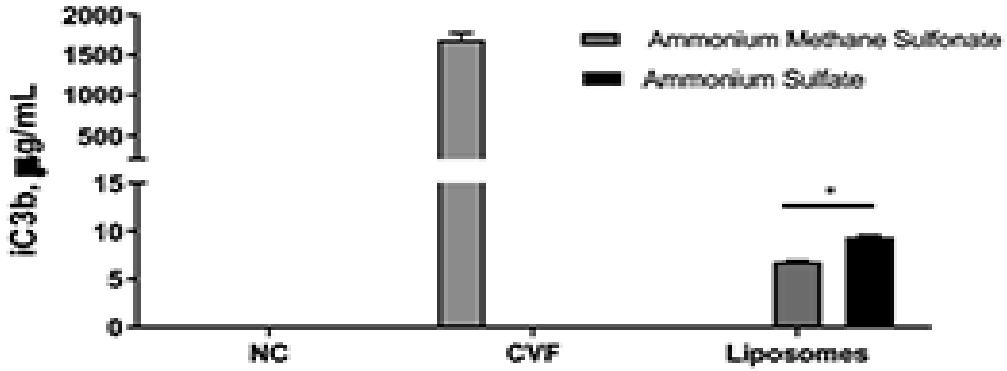
Chanan-Khan et al., (2003) Ann. Oncol., 14:1430-1437

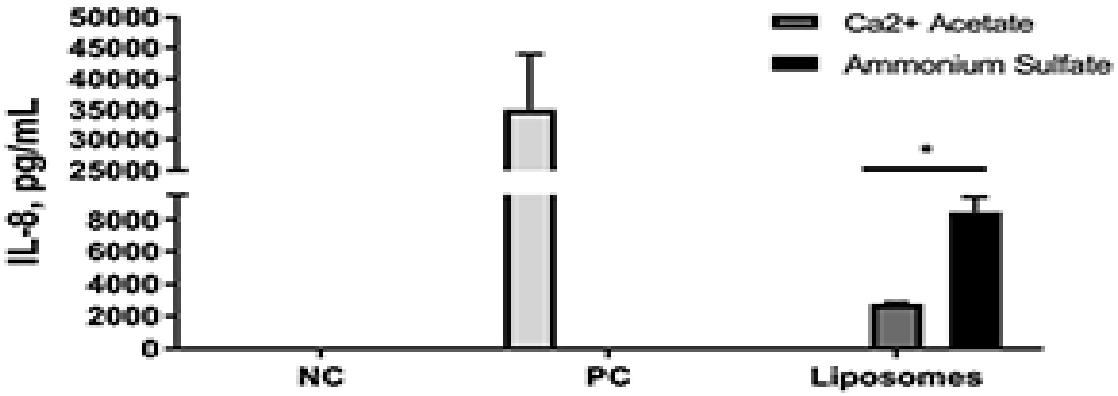
2nd generation liposomes

2nd Generation Liposomes Overcome Infusion Reactions

NCL Nanotechnology Characterization Laboratory | NCI Alliance for Nanotechnology in Cancer

Difference in Biological Response



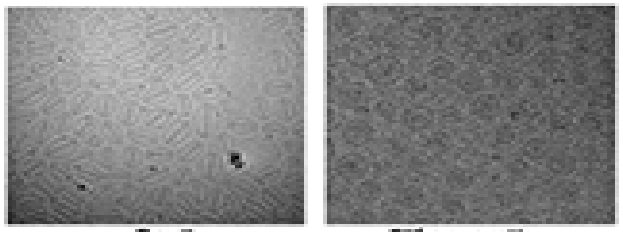


DXR=doxorubicin; NC= negative control; CVF= cobra venom factor; PEG = polyethylene glycol; PC = positive control

האוניברסיטה העברית בירושלים
THE HEBREW UNIVERSITY OF JERUSALEM

These data are generated in collaboration with Dr. Barenholz

Difference in shape



Doxil | 2nd generation

Allergenicity

ty: DTH to dendrimers

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A case of toxic epidermal necrolysis-like dermatitis evolving from contact dermatitis of the hands associated with exposure to dendrimers

Contact Dermatitis 2008: 59: 122–123

T. Toyama, H. Matsuda, I. Ishida, M. Tani, S. Kitaba, S. Sano and I. Katayama

Department of Dermatology, Course of Integrated Medicine, Graduate School of Medicine, Osaka University, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan

of necrotizing dermatitis (type IV reaction) in response to dendrimers is reported in the
r, chills, exudative erythema and fused bullae (Nikolsky's reaction)
n is unknown

Immunogenicity

Immunogenicity

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ENM approved for clinical use which resulted in antigenic response
None

Research-grade ENM *
for which antibody was generated
C60
C70
SWCNT
PAMAM-dendri
Liposomes

ENM carrying ThPr and resulting anti-ENP sponse
None

- **Nanoparticles Can Be Engineered To:**
  - Be (non)immunogenic
  - Reduce imunogenicity of therapeutic proteins
  - Enhance immunogenicity of proteins/peptides
- **Accidental Nanoparticles ≠ Nanomedicines**

Accidental particles contributing to antigenicity of ThPr
Glass fibers
Cellulose fibers
Tungsten
Silicon Oil
Rubber
Stainless steel
Fluoropolymers

ENM carrying ThPr and resulting in anti-ThPr response
None

ENM carrying ThPr and not resulting in anti-ThPr response
PEG-gold-TNFα (Cyt6091)
Liposome-streptokinase
PS-liposome-Factor VIII

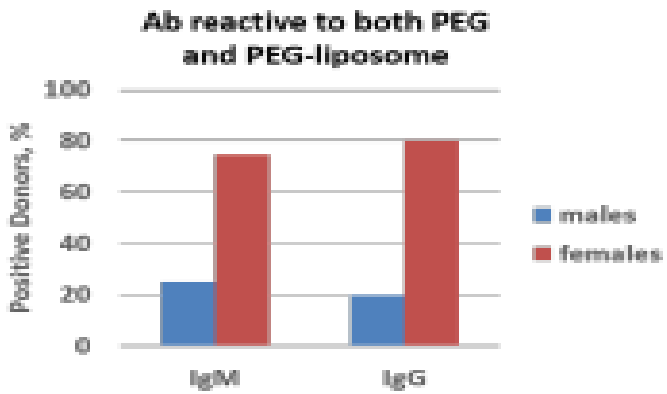
* - antibodies were generated ONLY after conjugation to protein carrier and injection in the presence of strong adjuvants
ENM = engineered nanomaterials; ThPr = therapeutic protein; SWCNT = single wall carbon nanotubes; PAMAM = polyamidoamine; TNF = tumor necrosis factor
Dobrovolskaia & McNeil. *Handbook of Immunological properties of engineered nanomaterials*. WSP, 2013, ISBN 978-981-4390-25-5.

Anti-PEG antibody

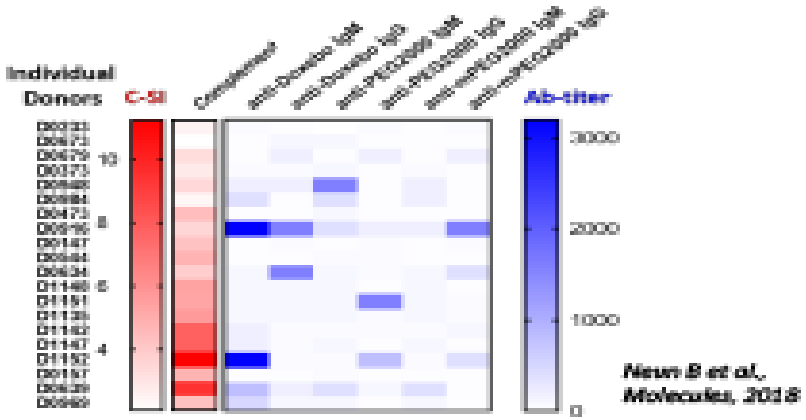
Pre-existing anti-PEG antibody

- PEGylation of nanoparticles is common to improve circulation time
- Several studies reported existence of naturally occurring antibody
- Functional significance of these antibodies is incompletely understood

"a high level of pre-existing anti-PEG antibodies was a major, but not the sole, factor necessary for triggering first-exposure allergic reaction to pegnivacogin, a PEGylated RNA aptamer" Ganson et al., J ALLERGY CLIN IMMUNOL MAY 2016



High (> 800) titer PEG-reactive antibodies are detected in both healthy males and females, but are more prevalent in females



Neun B et al., Molecules, 2018

PEG Ab titer does not correlate with complement activation by PEGylated liposomes. The Ab suggest greater risk but can't predict the reaction and its magnitude. Functional assay, e.g. C3 ELISA, should be used instead

Anti-inflammatory properties

Anti-inflammatory and immunosuppressive properties

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Mechanism of Action

Anti-inflammatory

Indirect

1. ***Carriers for anti-inflammatory drugs***
   (corticosteroids, indomethacin, methotrexate)
   liposomes, dendrimers, polymeric NP

2. ***Carriers for anti-cytokine agents***
   (receptors' antagonists, siRNA against cytokines and signaling molecules, DNA of anti-inflammatory cytokines) polymeric NP, dendrimers, liposomes, chitosan NP

3. ***Anti-adhesion agents***
   (siRNA against CCR2, selectins' antagonists)
   lipid NP, dendrimer-like polymers

Direct

1. ***Inhibition of COX and pro-inflammatory signaling***
   PAMAM dendrimers, gold NP

2. ***Anti-oxidant activity***
   cerium oxide NP, gold NP, fullerene derivate

3. ***Anti-cytokine activity***
   gold NP

Immunosuppressive

Indirect

1. ***Carriers for traditional immunosuppressive drugs***
   (cyclosporine, tacrolimus, rapamycin, mycophelic acid) liposomes, polymeric NP, lipid NP

2. ***Toleregenic vaccines***
   (antigens, co-stimulatory signals) polymeric NP, iron oxide NP, PEG-gold NP, chitosan NP

3. ***Myelosuppression***
   (increase toxicity of a carried drug)
   PIBCA, PIHCA

Direct

1. ***Inhibition of T-cell-mediated immunity***
   iron oxide NP, fullerene 60

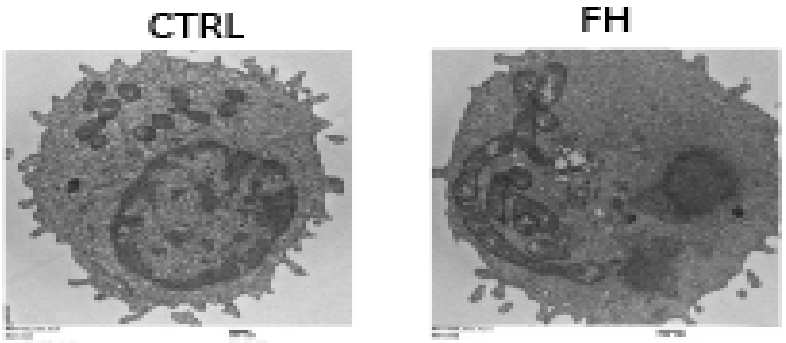
2. ***Interference with functions of the cells of the immune system***
   iron oxide NP, PVA-SPION, MWCNT, quantum dots

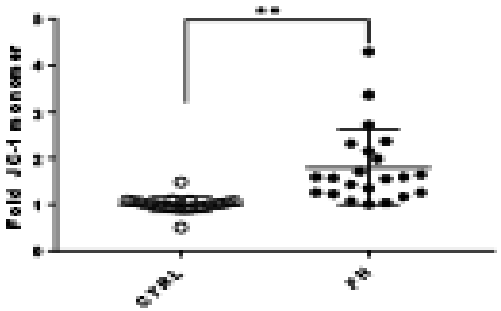
3. ***Myelosuppression and toxicity to cells of the immune system***
   Sb_2O_3, Co, ZnO, TiO_2 NP

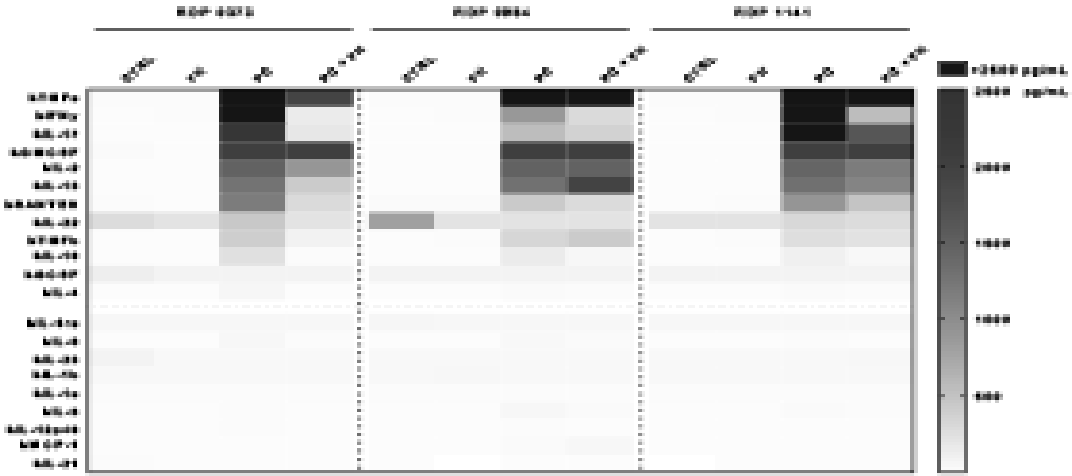
Mechanism of Action

Immunosuppression

Immunosuppression

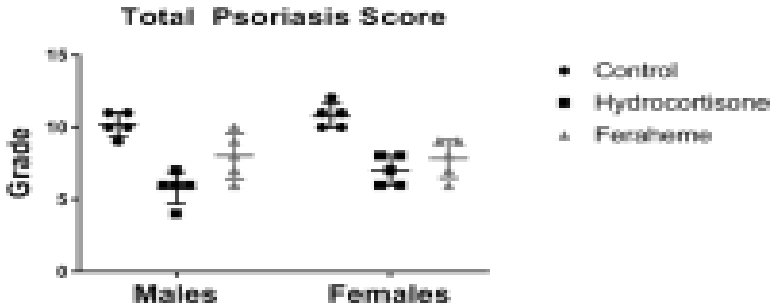






Iron oxide nanoparticles (Feraheme) suppresses activation of T-cells via a mechanism involving mitochondrial ROS in vitro

Shah et al., Toxicology and Applied Pharmacology, 2018

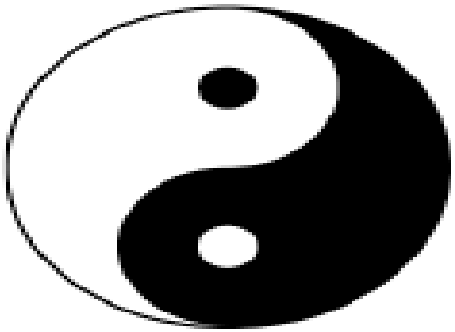


Topical application of Feraheme inhibits development of skin lesions in a mouse model of psoriasis

Shah et al., Precision Nanomedicine, 2019

Take home message

Take Home Message



- Immunotoxicity can be GOOD or BAD
- Depends on whether it is desirable (intended) or undesirable (unintended)

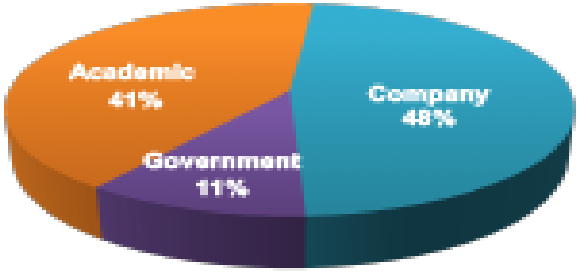
- Nanoparticles can be engineered to improve desirable properties or to reduce undesirable ones

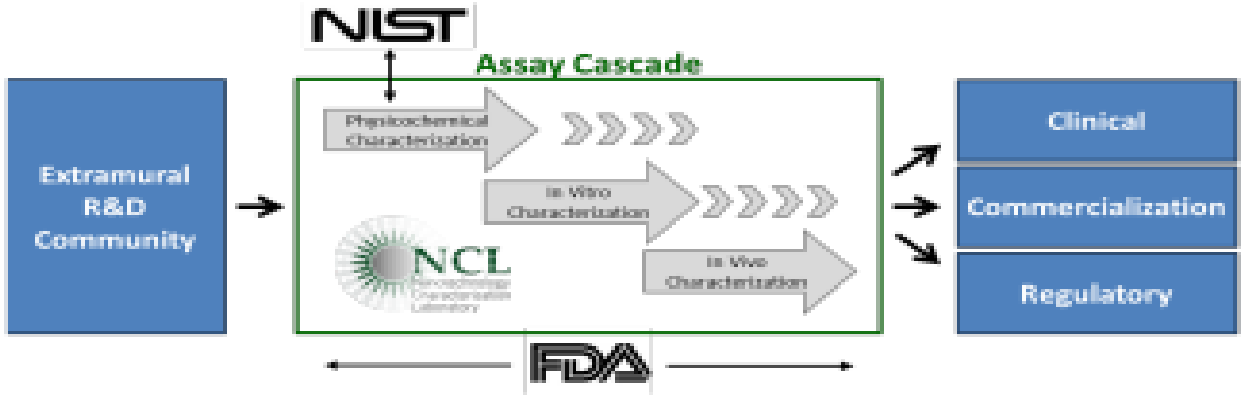
- Understanding SAR and mechanisms of toxicity can inform creation of safe and efficient complex drug systems

Nanotechnology characterization lab

Nanotechnology Characterization Lab

FREE Service for cancer nanotechnology concepts, by application.





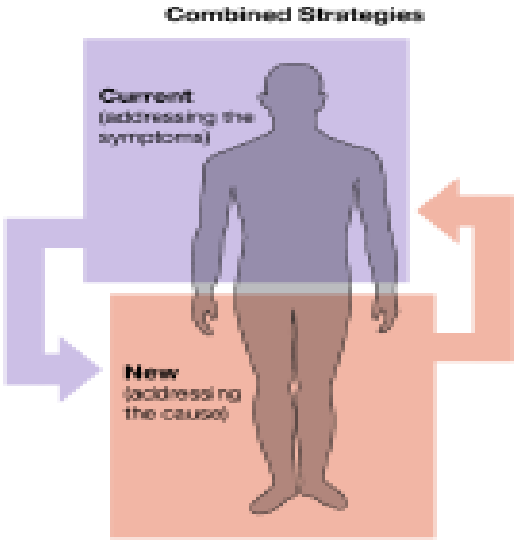
> 130 Assay Cascade projects
> 400 nanoparticles characterized
15 collaborations advanced to clinical trials
2 received regulatory approval

NCL has 15 years of knowledge and expertise in nanoparticle characterization and helps accelerate the translation of promising nanotech drugs and diagnostics.

60+ protocols available for research community online: https://ncl.cancer.gov/resources/assay-cascade-protocols

Future directions

Future Directions



- Many directions available to cover gaps, overcome biological barriers, improve delivery, safety&efficacy
- One important direction – overcoming infusion reactions

Szebeni J., et al., Nature Nanotechnology, 2018

NCL team

NCL Team

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Siva Dasa
Marina Dobrovolskaia
Matthew Hansen
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Barry Neun
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Sarah Skoczen
Kelsie Snapp
Stephan Stern
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Funded by NCI Contract HHSN261200800001E

National Cancer Institute
Frederick National Laboratory for Cancer Research

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NCL immunology team

Special Thanks to the NCL Immunology Team

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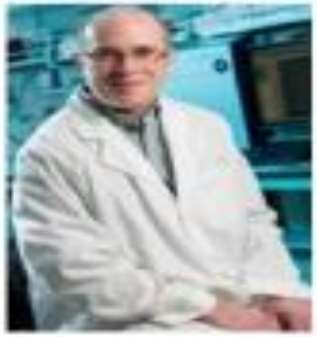
Current Members

Barry Neun



Edward Cedrone

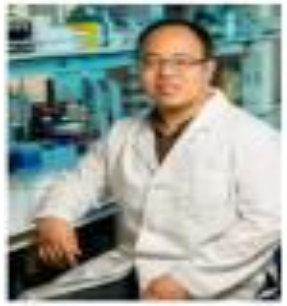
Timothy M. Potter

Alumni

Anna Ilinskaya

Jamie Rodriguez

Parag Aggarwal



Enping Hong

Ankit Shah