Nanotechnology for medical applications

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

- 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

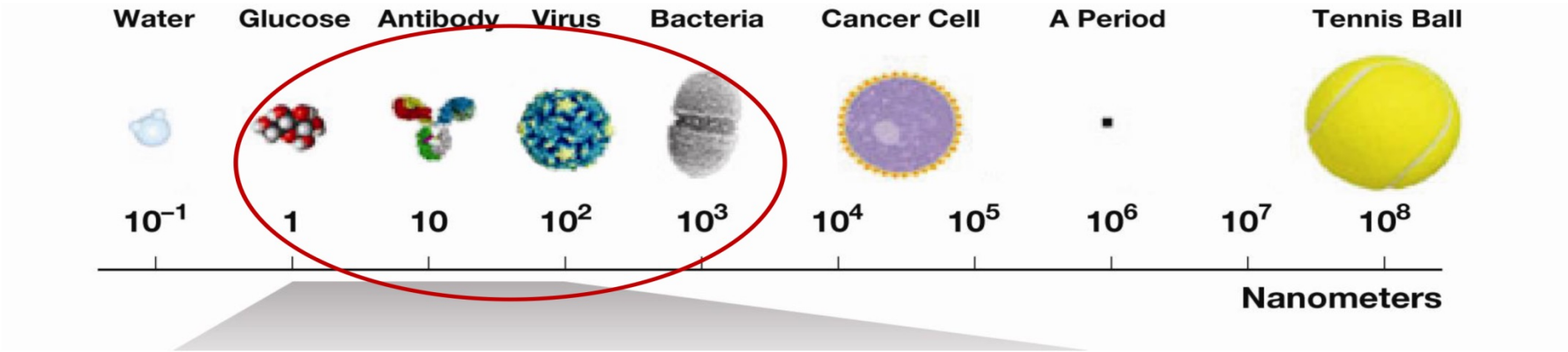
What is nano?

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)

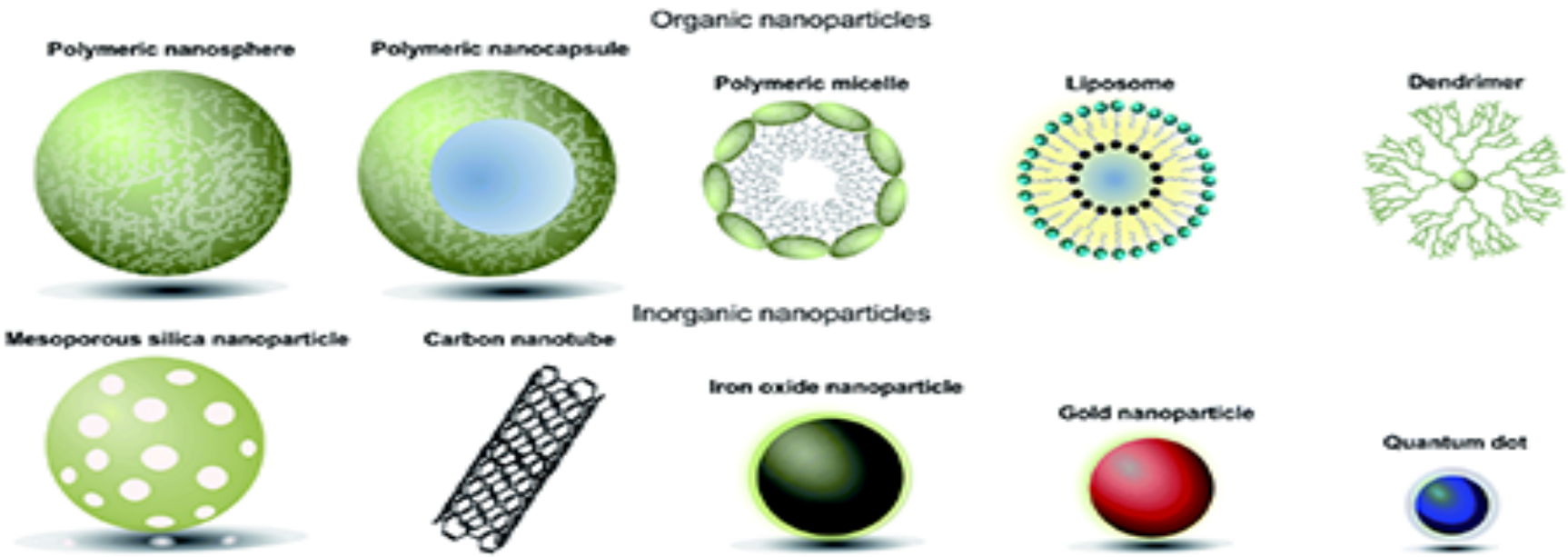
"Whether a material or end product is engineered to exhibit properties or phenomena, including physical or chemical properties or biological effects, that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to one micrometer (1,000 nm)"(US FDA)



Examples of nanomaterials

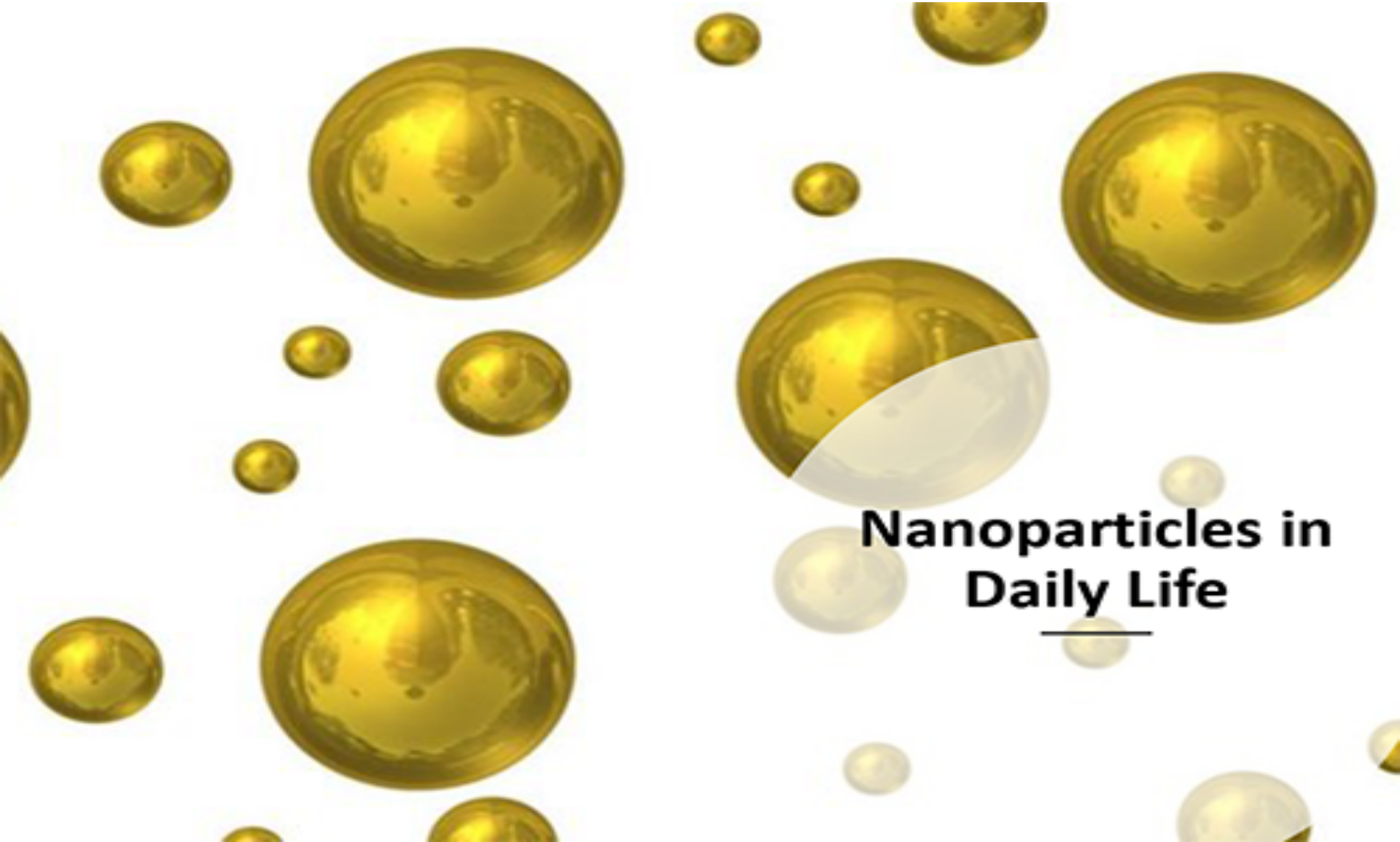
Examples of Nanomaterials

NCL Nanotechnology Characterization Laboratory | NCI Alliance for Nanotechnology in Cancer



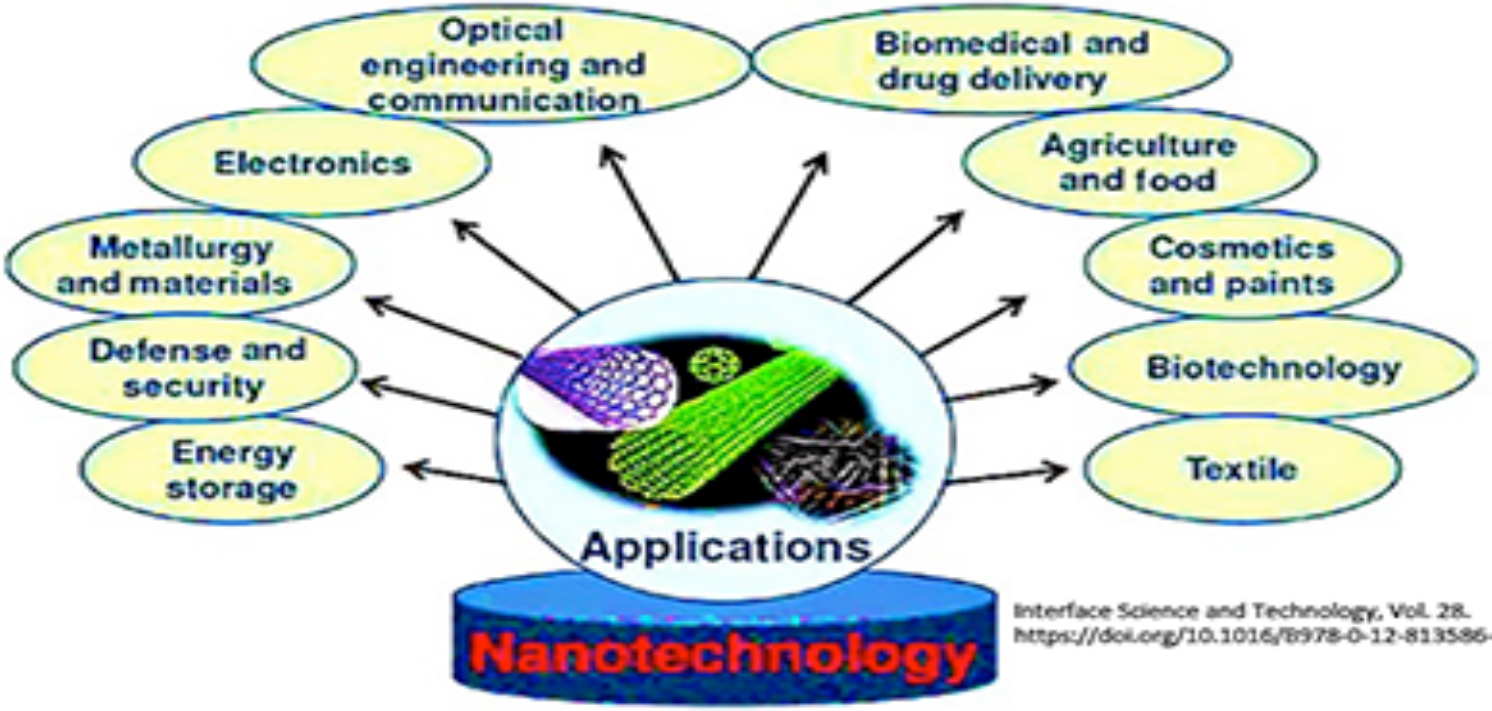
Richards D.A., Chem. Sci., 2017, 8, 63

Nanoparticles in daily life

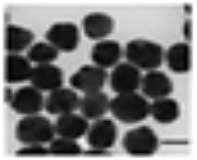


Nanoparticles

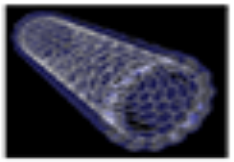
Nanoparticles in Daily Life



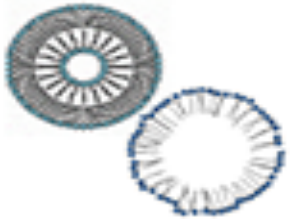
Interface Science and Technology, Vol. 28.
https://doi.org/10.1016/B978-0-12-813586-0.00004-3



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)

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)

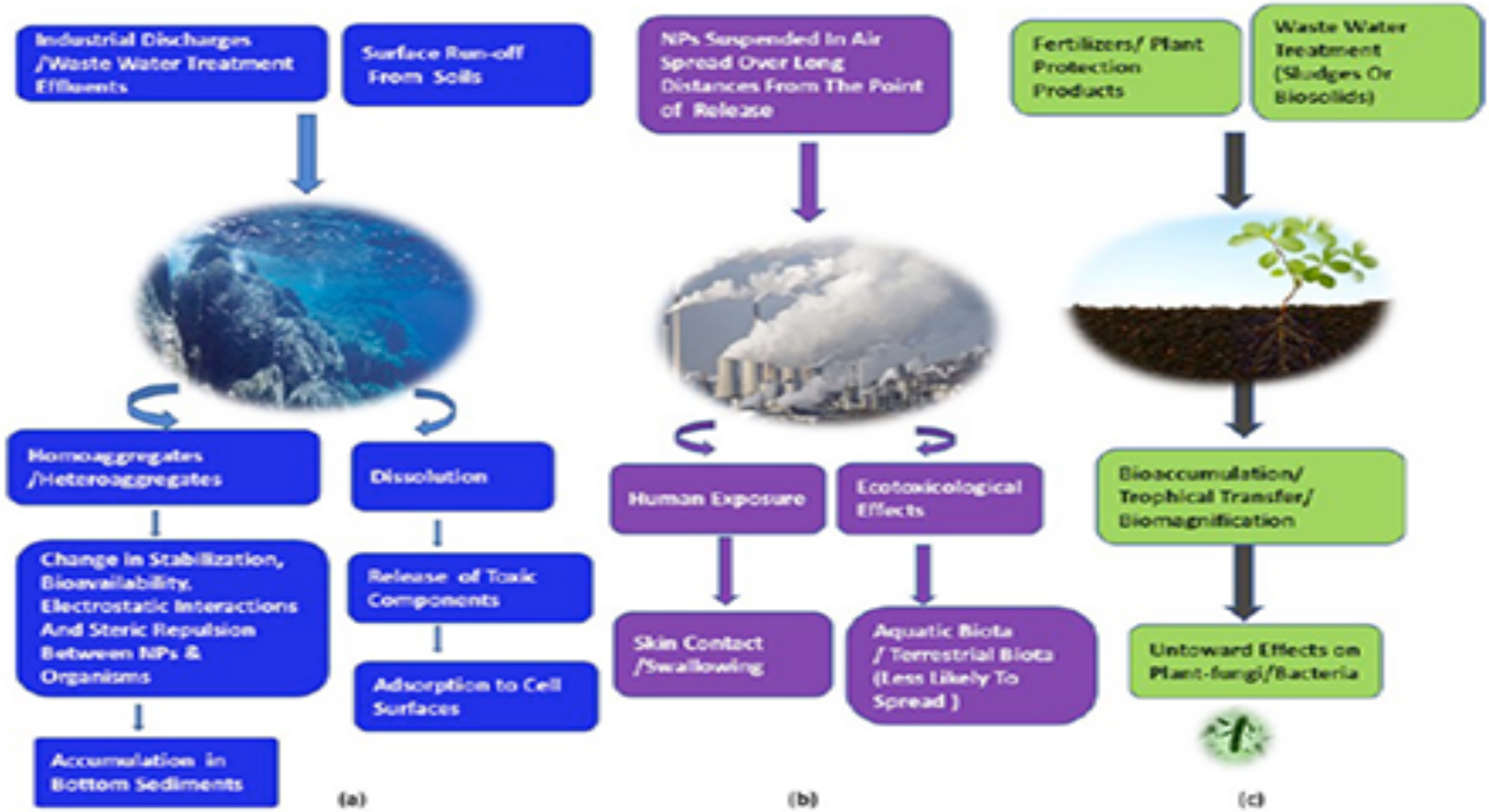
10 Angstroms is dedicated to bringing innovative systems and equipment to the nanotechnology R&D market. The company provides both sales representation and servic for advanced instrumentation companies.

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

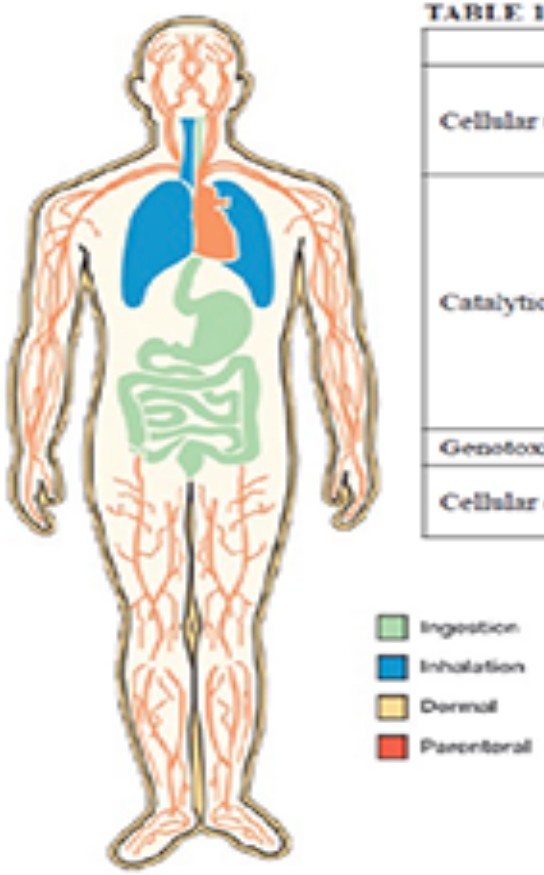


TABLE 1: Mechanisms of engineered nanoparticle toxicity

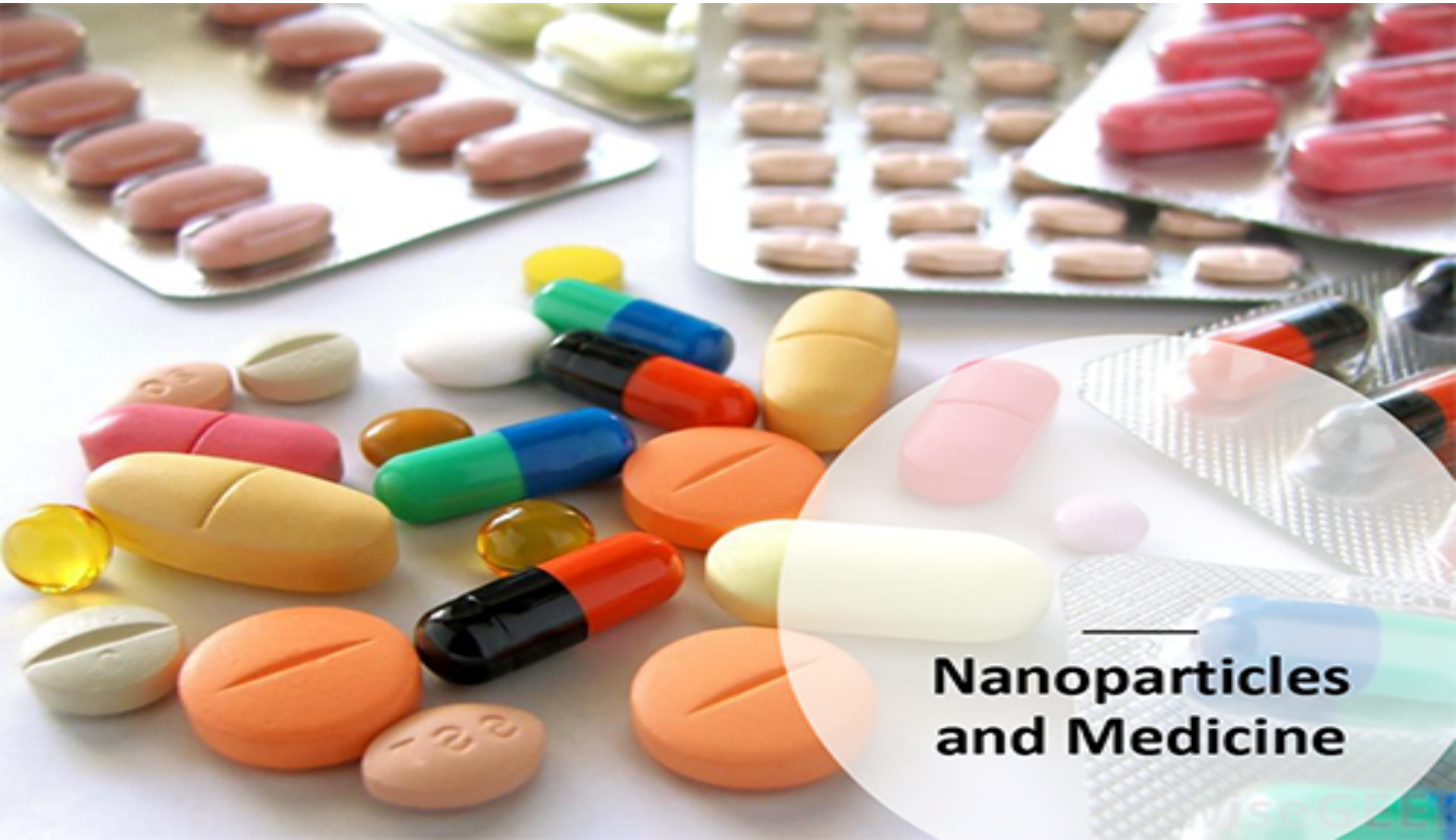
Mechanisms of toxicity		Reference number
Cellular uptake	Direct intracellular entry	119
	Cell membrane binding	120
	Uptake through reticuloendothelial system	121
Catalytic activity	Release of more reactive ionic form from nanoparticle surface	60
	ROS generation, oxidative stress	24, 122
	Lipid peroxidation	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



Medical applications

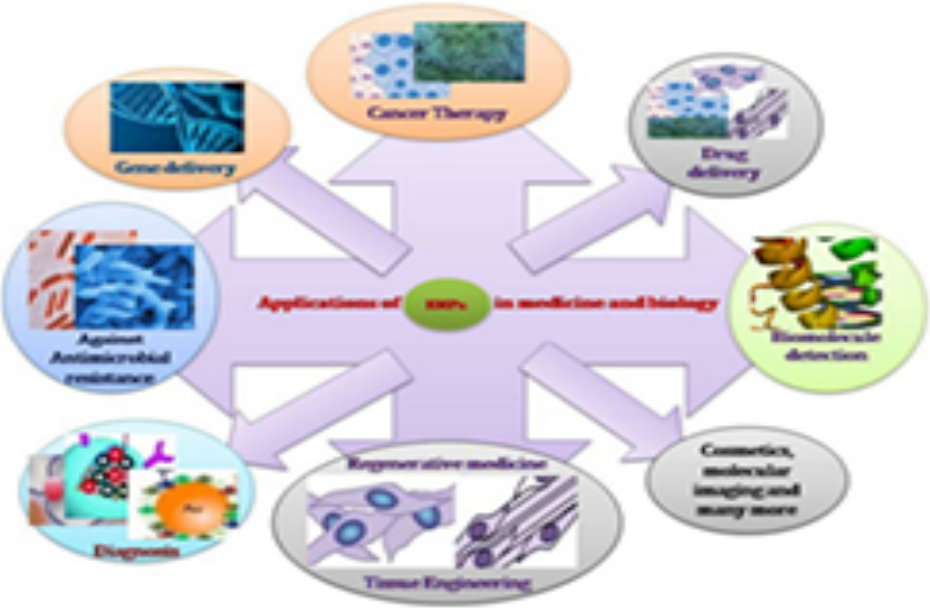
Nanoparticles for Medical Applications

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

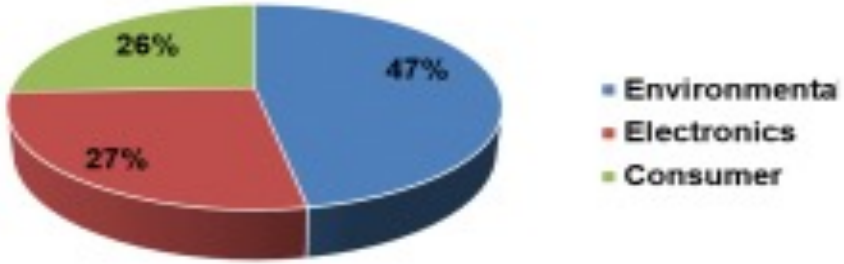


Rudramurthy, G. R. and M. K. Swamy (2018). JBIC Journal of Biological Inorganic Chemistry 23(8): 1185-1204.

Evolving landscapes

Evolving Landscape of Nanotechnology Products

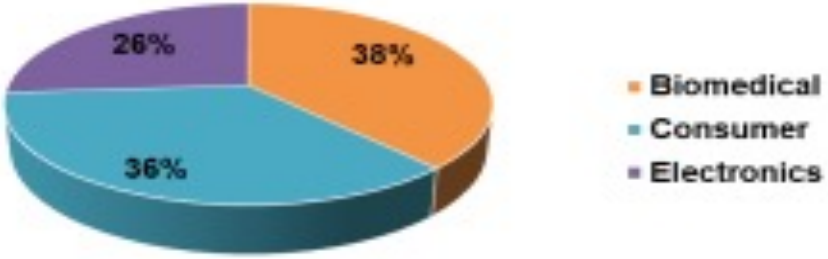
Global Nanotechnology Market (2015)



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

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

CAGR rates (2016-2021)

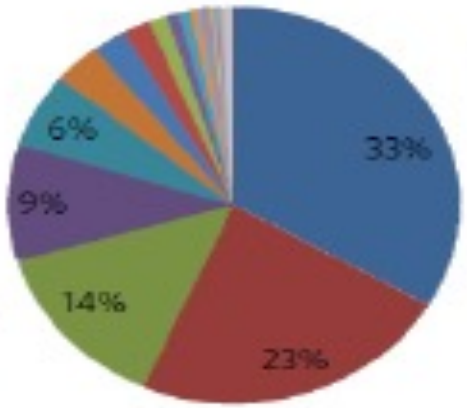


Biomedical Applications of Nanotechnology are predicted to have the highest 5-year compound annual growth rate by 2021

- 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

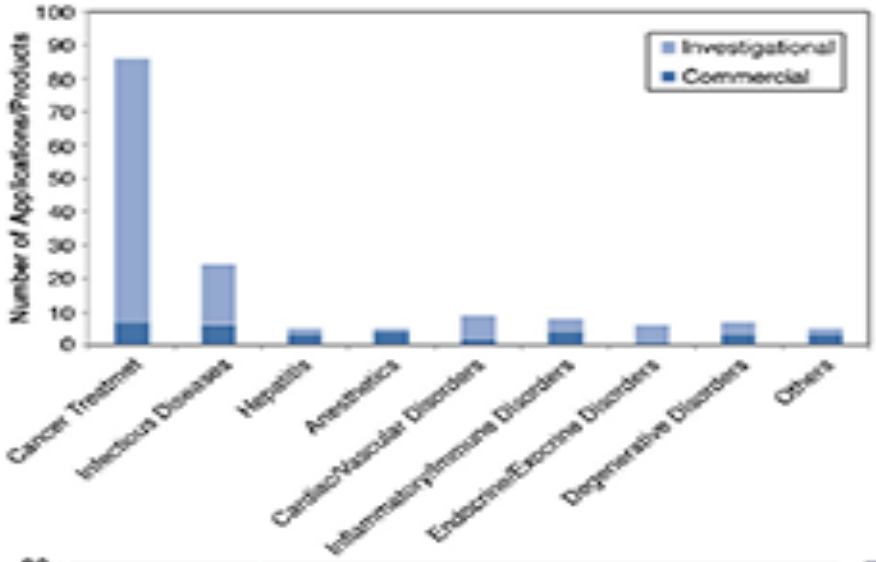
(1973-2015)

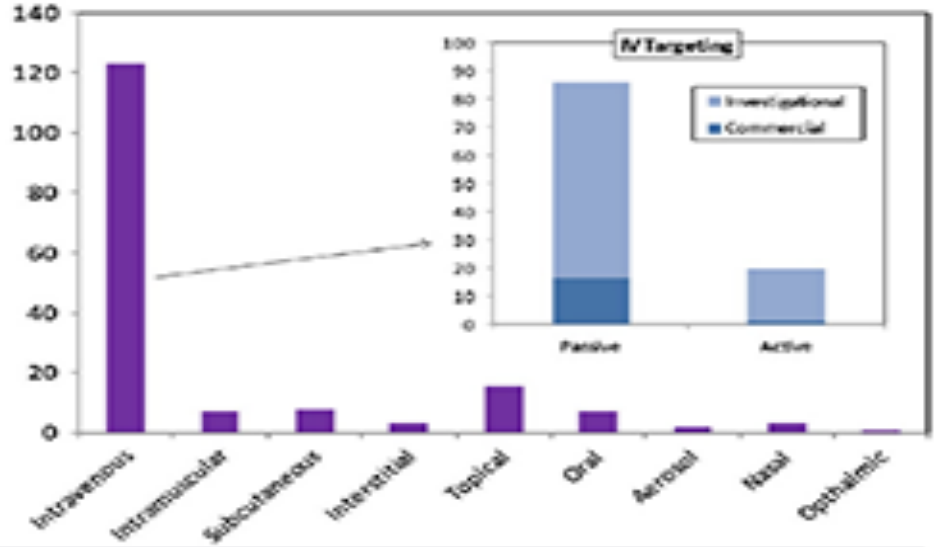


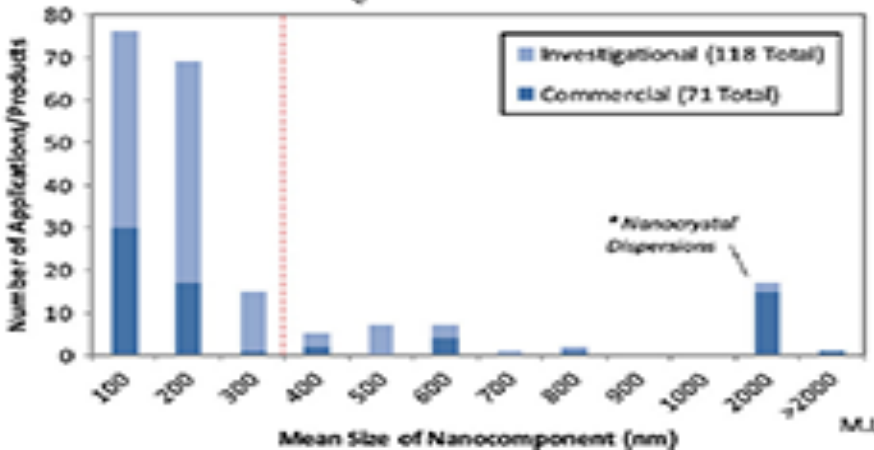
Liposomes, Nanocrystals and Emulsions dominate current nanomedicine landscape

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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Chemotherapy benefits

Benefits: chemotherapy

Experimental Hematology & Oncology

RESEARCH Open Access

Comparison of safety and toxicity of liposomal doxorubicin vs. conventional anthracyclines: a meta-analysis

Shamuldeen M Rafiyath[1], Mohammad Rasul[1], Byung Lee[1], Guoqing Wei[2], Gurpreet Lamboo[1] and Delong Liu[1*]

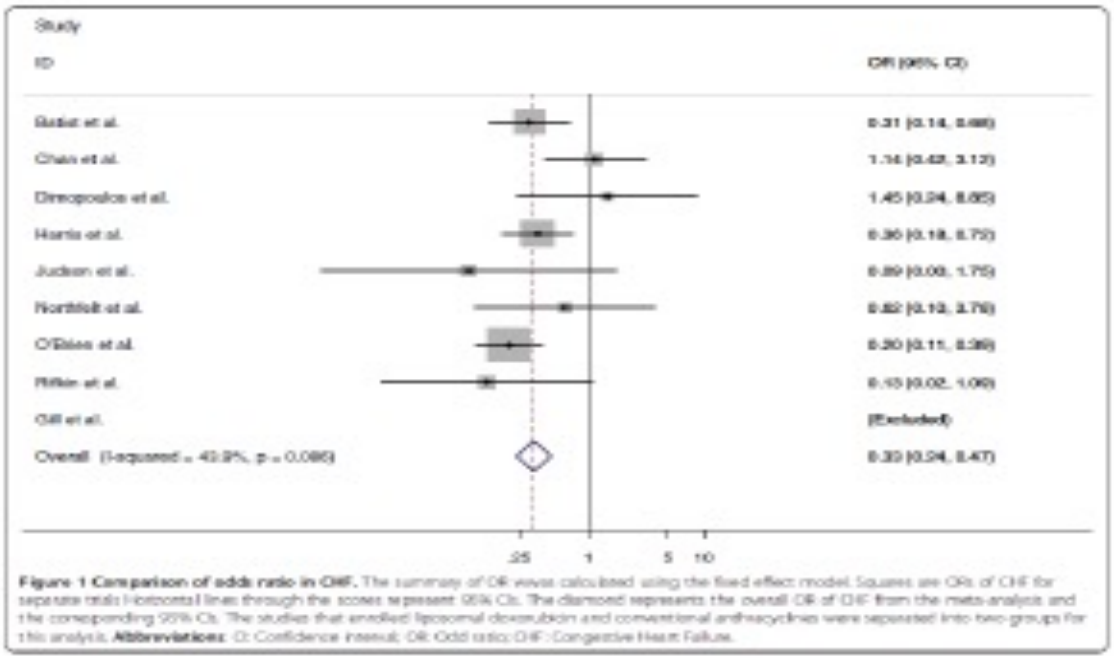
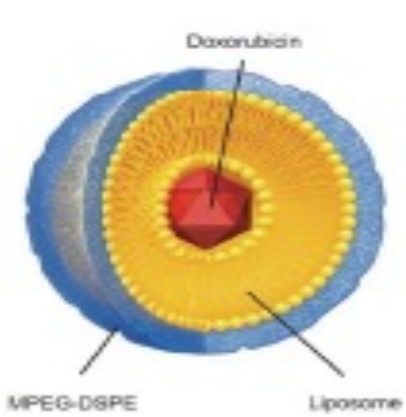


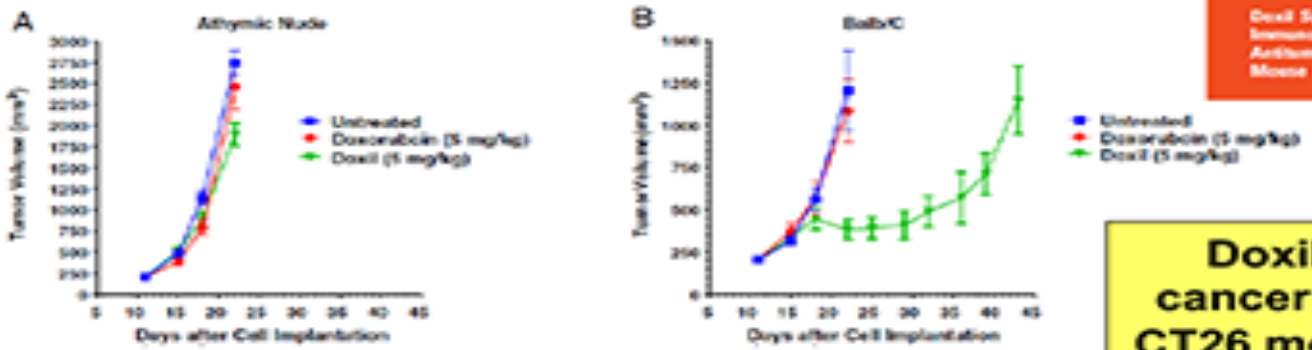
Figure 1 Comparison of odds ratio in CHF. The summary of OR were calculated using the fixed effect model. Squares are ORs of CHF for separate trials. Horizontal lines through the scores represent 95% CIs. The diamond represents the overall OR of CHF from the meta-analysis and the corresponding 95% CIs. The studies that enrolled liposomal doxorubicin and conventional anthracyclines were separated into two groups for this analysis. **Abbreviations:** CI: Confidence interval; OR: Odd ratio; CHF: Congestive Heart Failure.



Doxil (doxorubicin formulated using PEGylated liposome) is less cardiotoxic than free doxorubicin

Immunotherapy

Benefits: Immunotherapy



NEOPLASIA

Doxil Synergizes with Cancer Immunotherapies to Enhance Antitumor Responses in Syngeneic Mouse Models

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

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

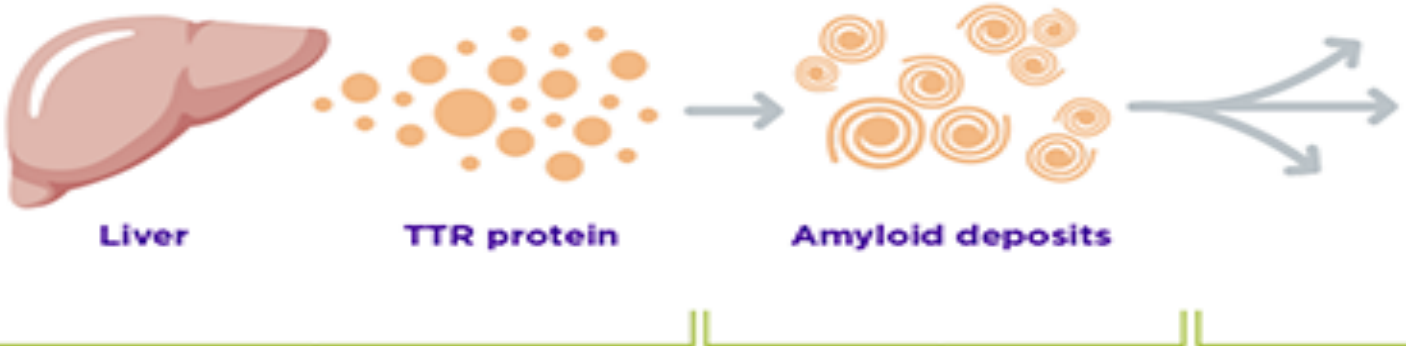
A Phase 1, Open-Label, Multicenter, Safety Study of Nivolumab (BMS-936558) in Combination With Nab-Paclitaxel Plus or Minus Gemcitabine in Pancreatic Cancer, Nab-Paclitaxel / Carboplatin in Stage IIIB/IV Non-Small Cell Lung Cancer or Nab-Paclitaxel in Recurrent Metastatic Breast Cancer (NCT02309177)

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**

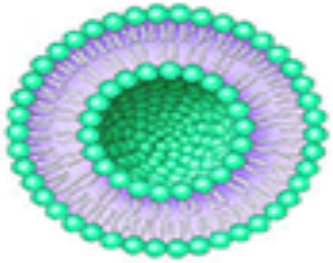
Amyloid deposits build up in different parts of the body, leading to symptoms of hATTR amyloidosis

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

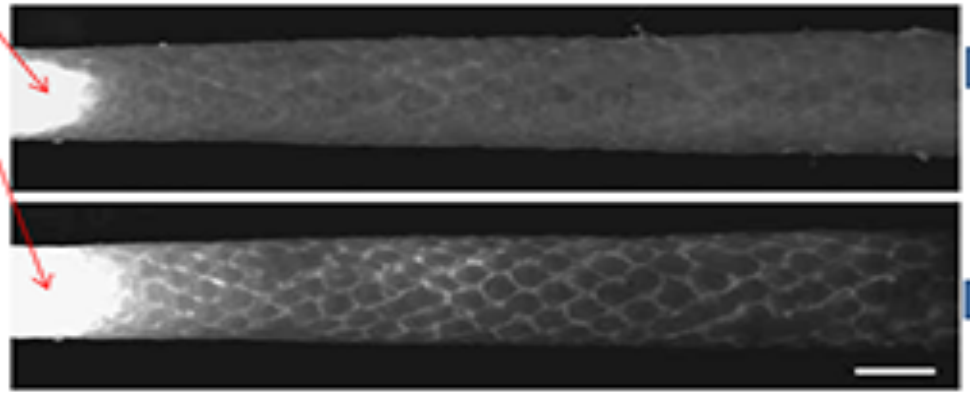
- i.d. injection
- Examine draining lymph nodes

Injection Site

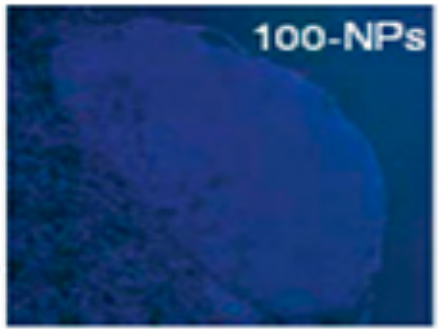
Tail

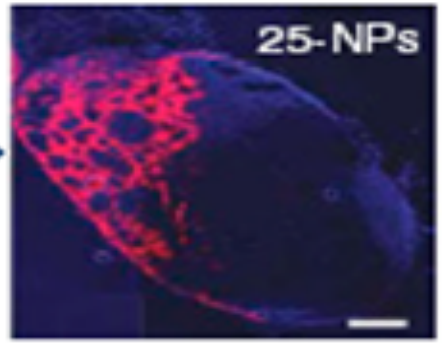
100nm

25nm



Draining lymph nodes





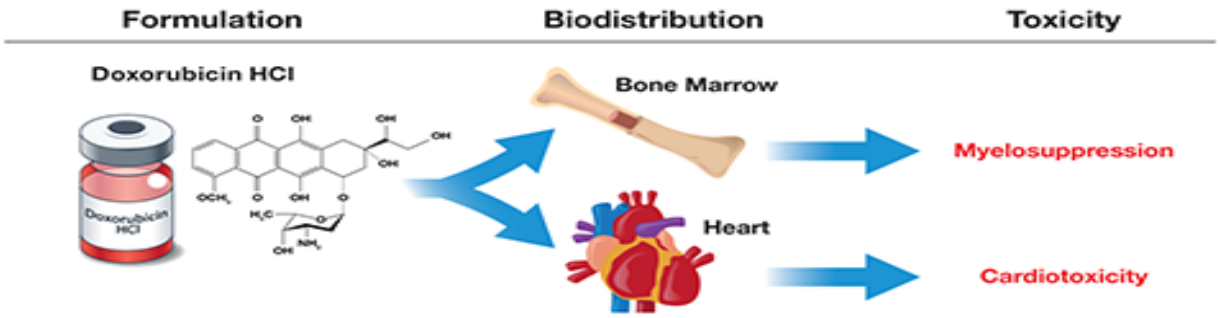
Smaller particles travel through lymphatics. Larger particles do not.

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

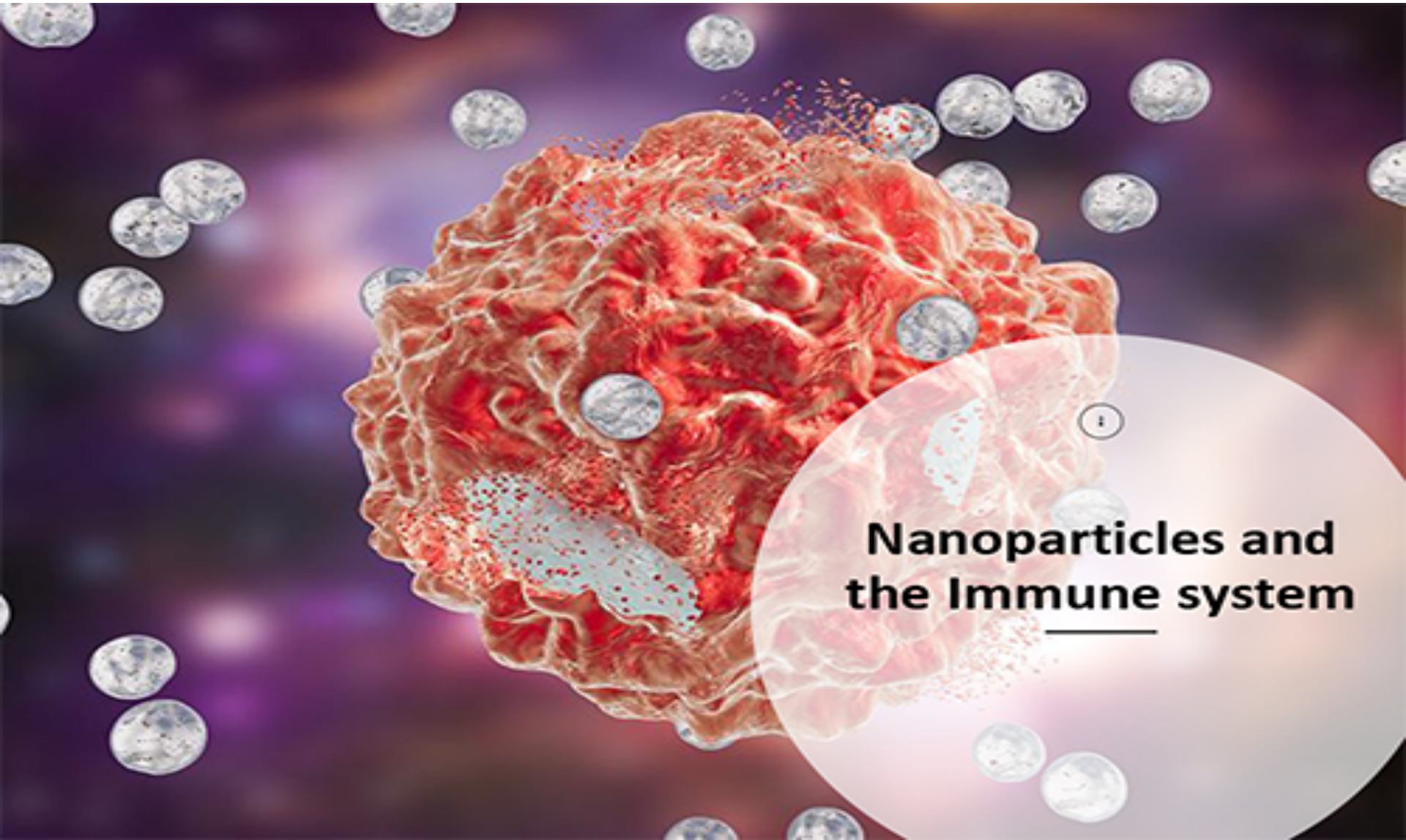
Toxicity

Concerns: Toxicity



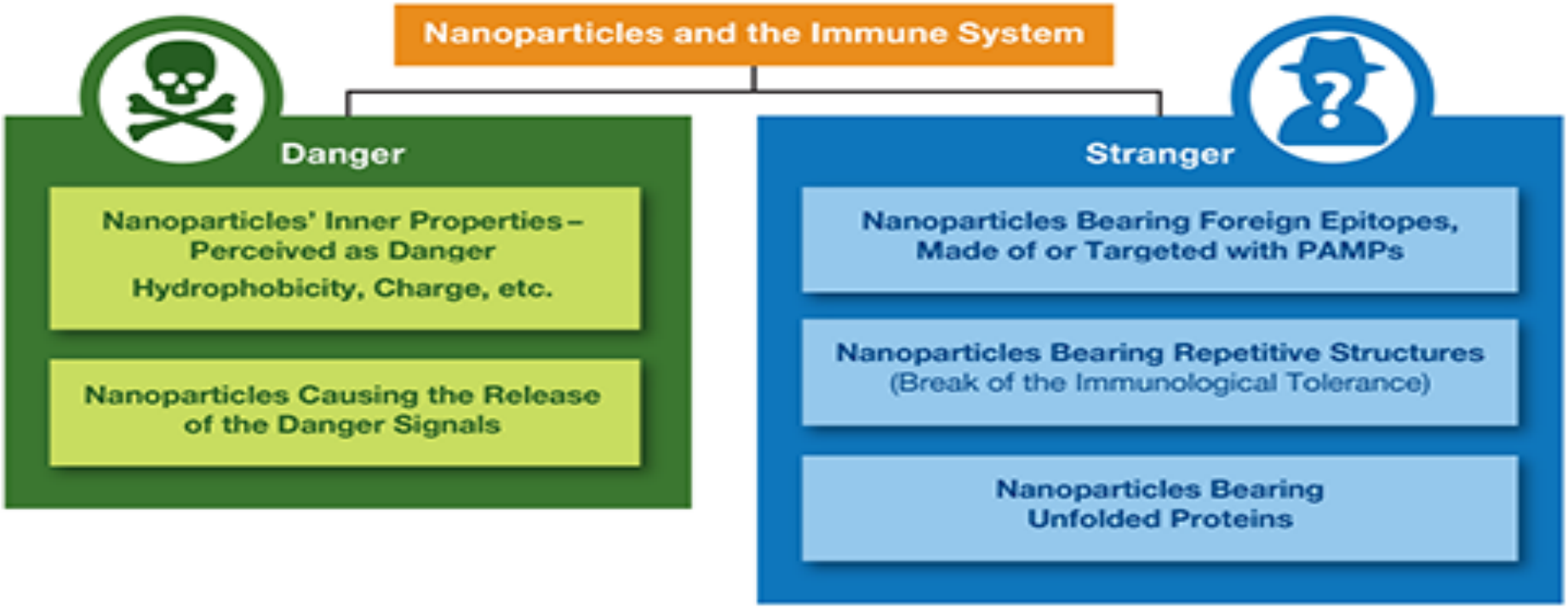
- Both nanocarrier and API can be toxic
- API toxicity can "relocate" depending on the particle biodistribution

Nanoparticles



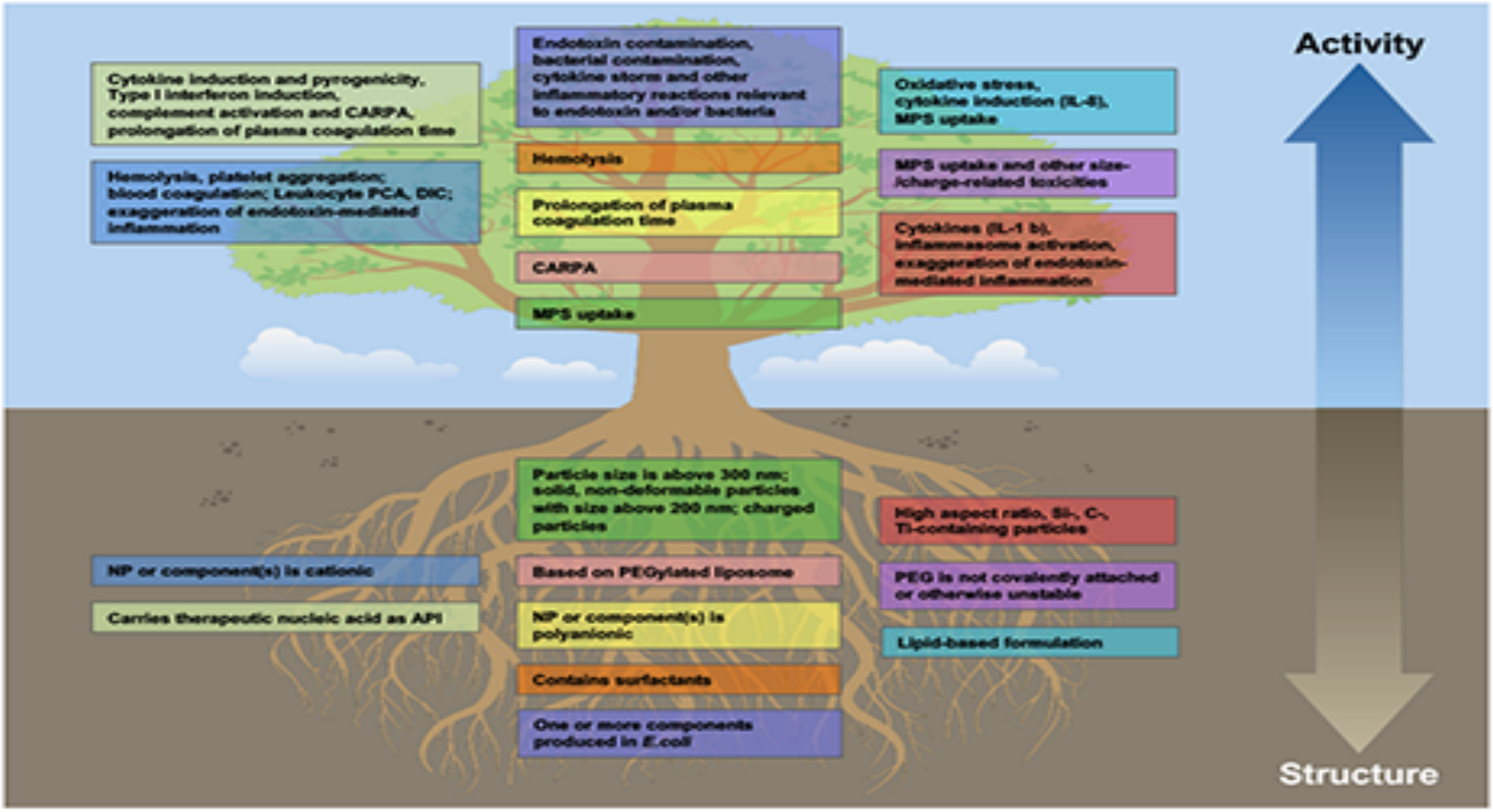
Immune system

Nanoparticles and the immune system



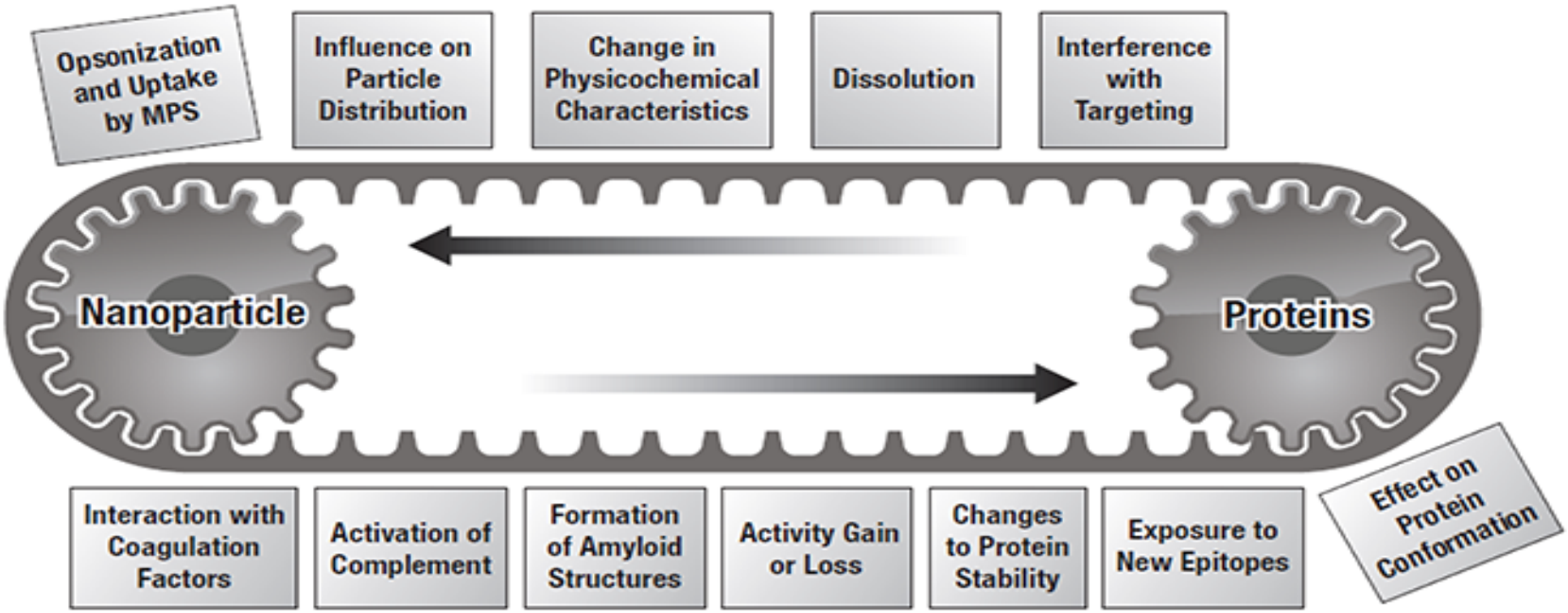
Structure activity relationship

Structure Activity Relationship



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

Protein binding

Protein binding affects particle size

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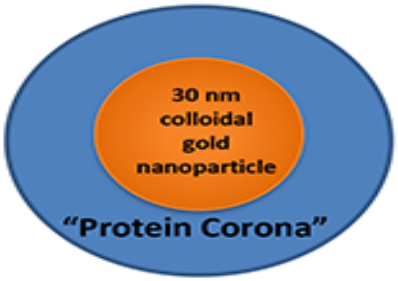
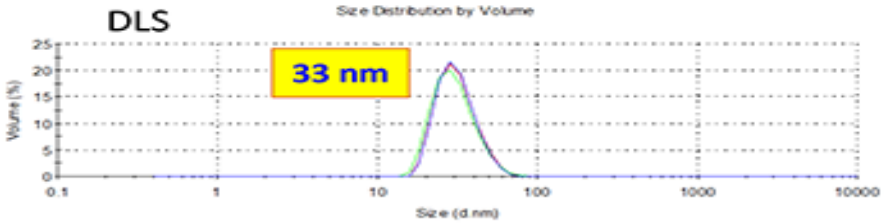
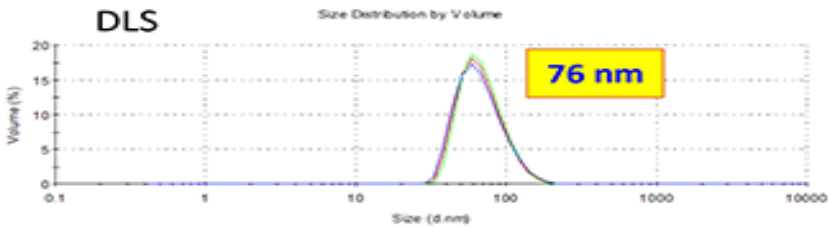
BEFORE

AFTER





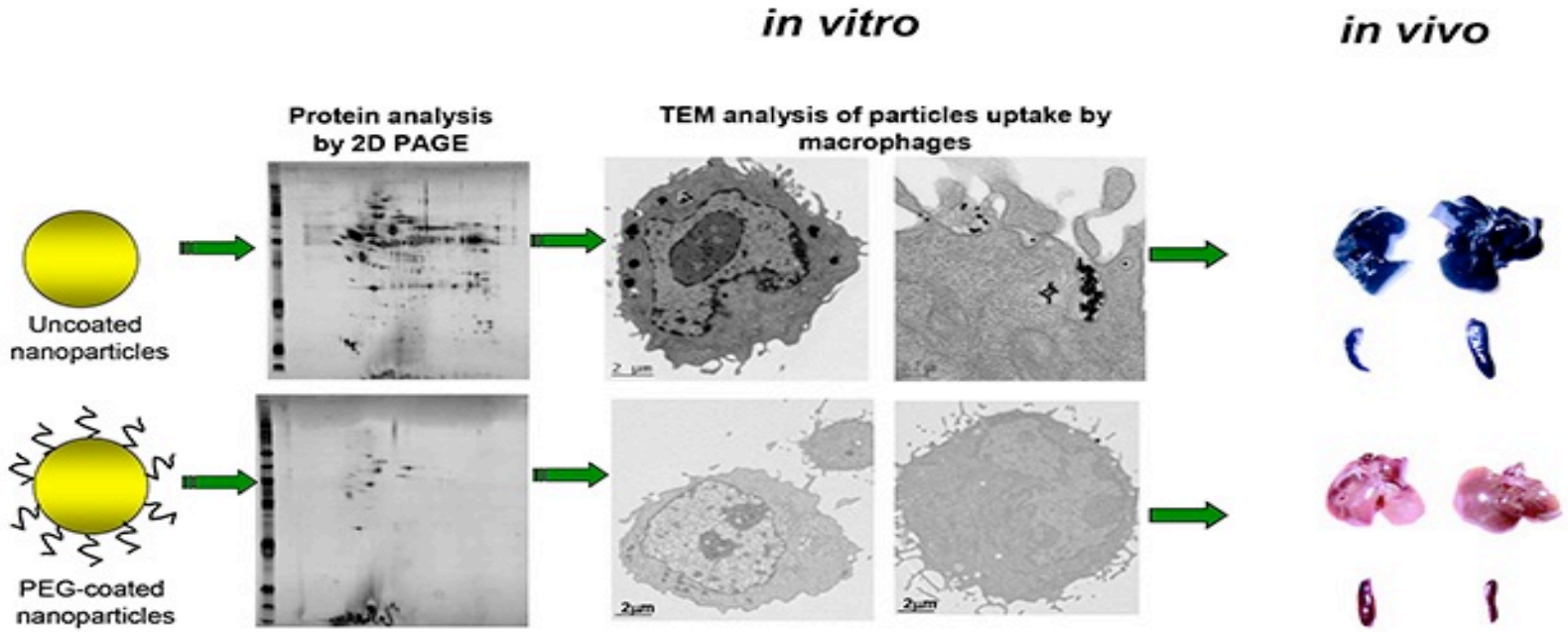


Incubation with human plasma increases hydrodynamic size of nanoparticles

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

Biodistribution

Protein Binding and biodistribution



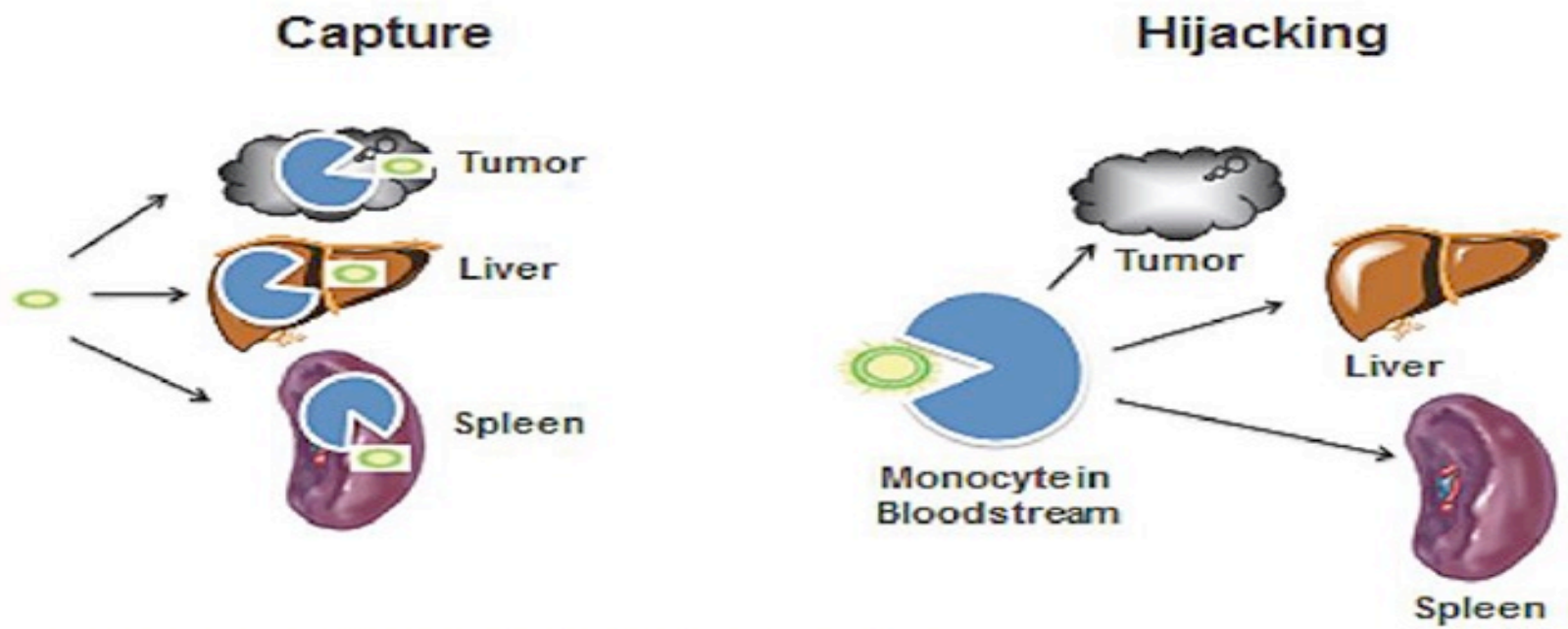
Dobrovolskaia et al., (2008), Mol.Pharm., 5:487-495.

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/ntno.30052

Cationic liposomes

Cationic Liposomes induce broad spectrum of cytokines

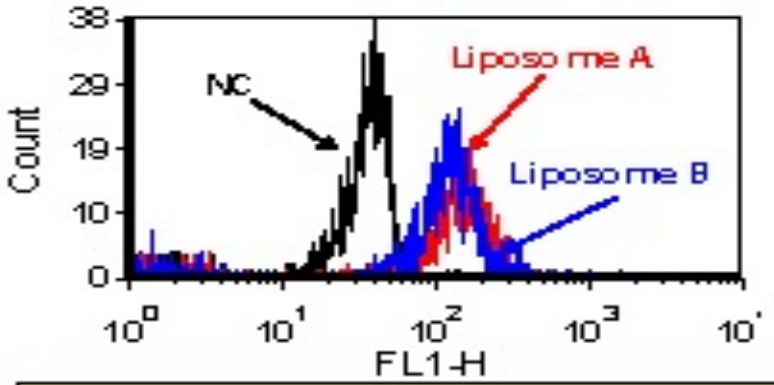
Cationic Liposomes

	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 dangersignals	MMP-1	MMP-7	MMP-9
Group:	metalloproteinases		

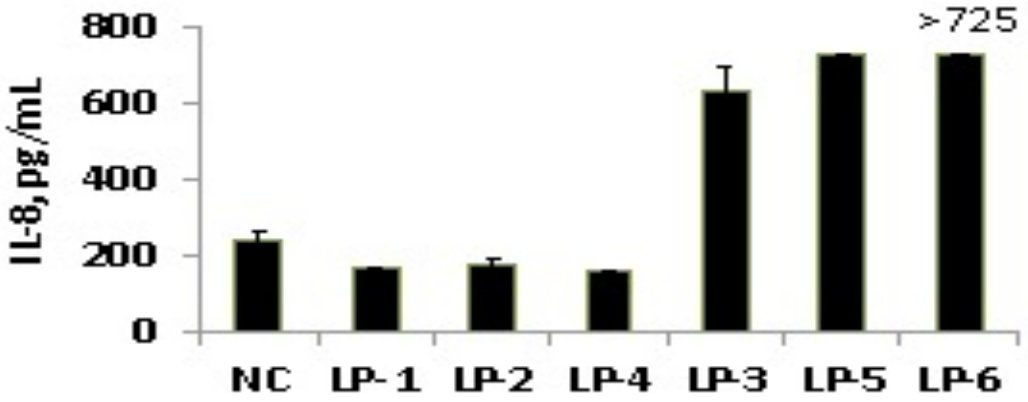
- Cationic liposomes induce wide range of pro-inflammatory responses
- While cytokines are needed for adjuvanticity, excessive secretion of some of them (e.g. TNFa) often leads to side effects (necrosis at the injection site)

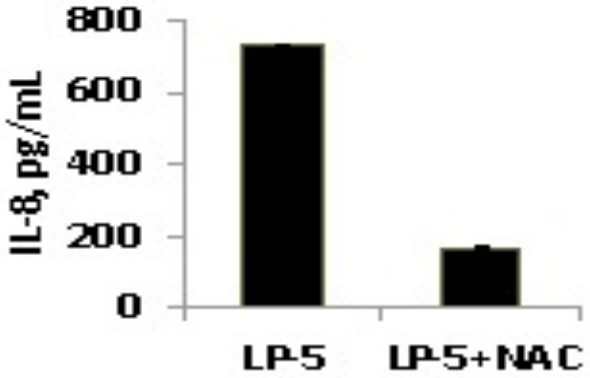


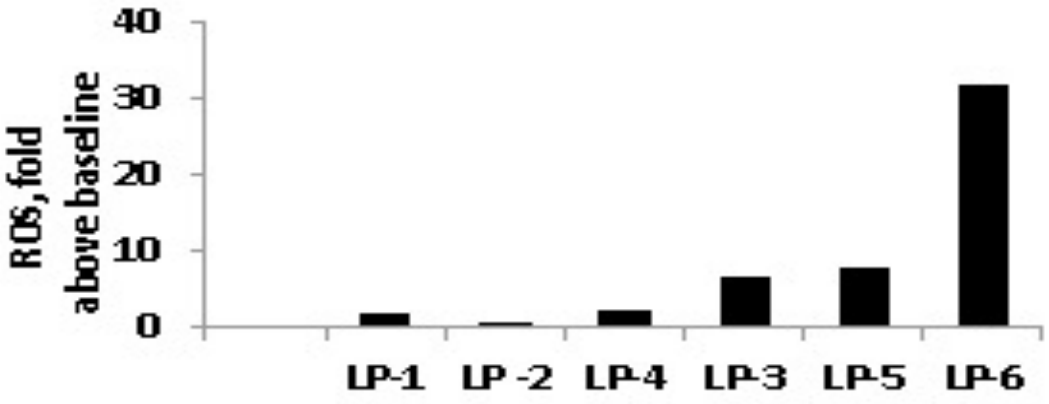
Oxidative stress is underlying mechanism

Anionic liposomes

Anionic liposomes induce chemokines







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

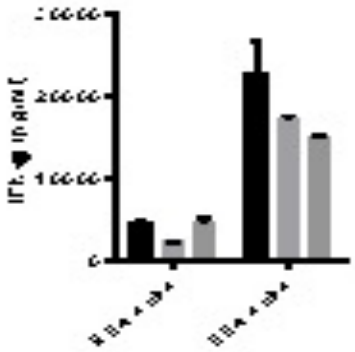
IFN

Nucleic Acid Nanoparticles induce IFN



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

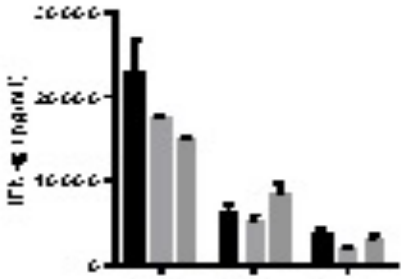
Composition

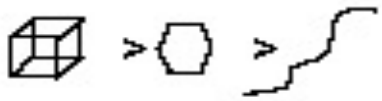


DNA < RNA

RNA nanoparticles are more potent than DNA nanoparticles

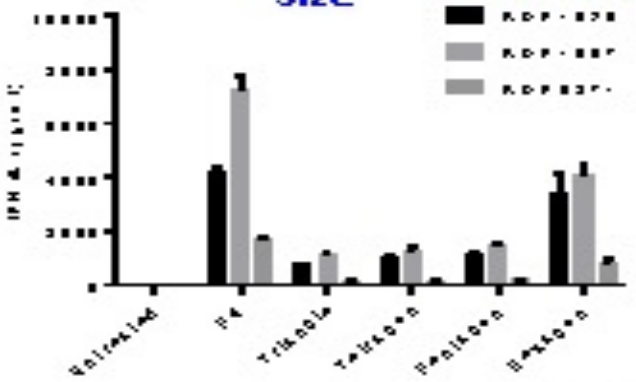
Architecture

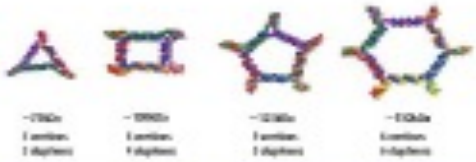




Globular particles are more potent than planar than fibrous particles

Size



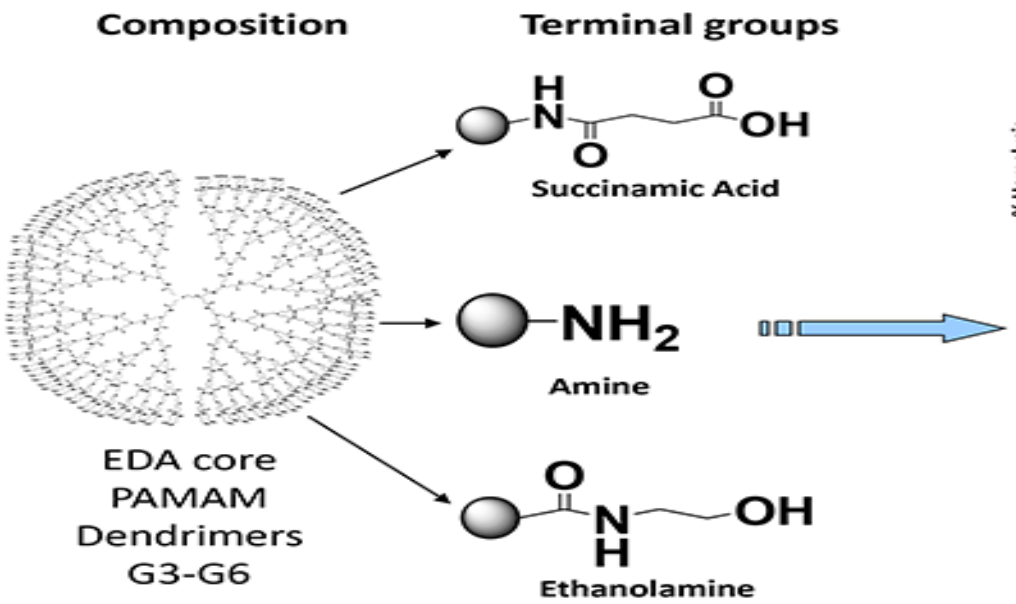


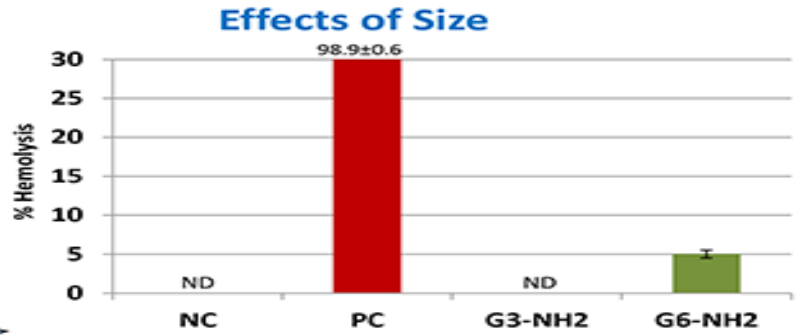
Larger particles are more potent their smaller particles

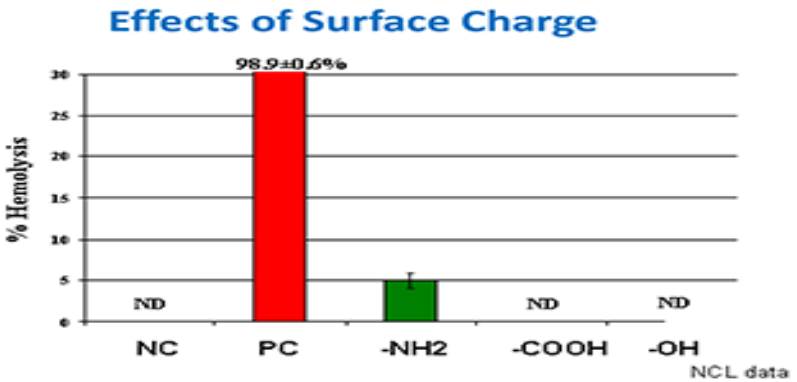
Hong E, et al. Nanoletters 2018

Hemolysis

Hemolysis







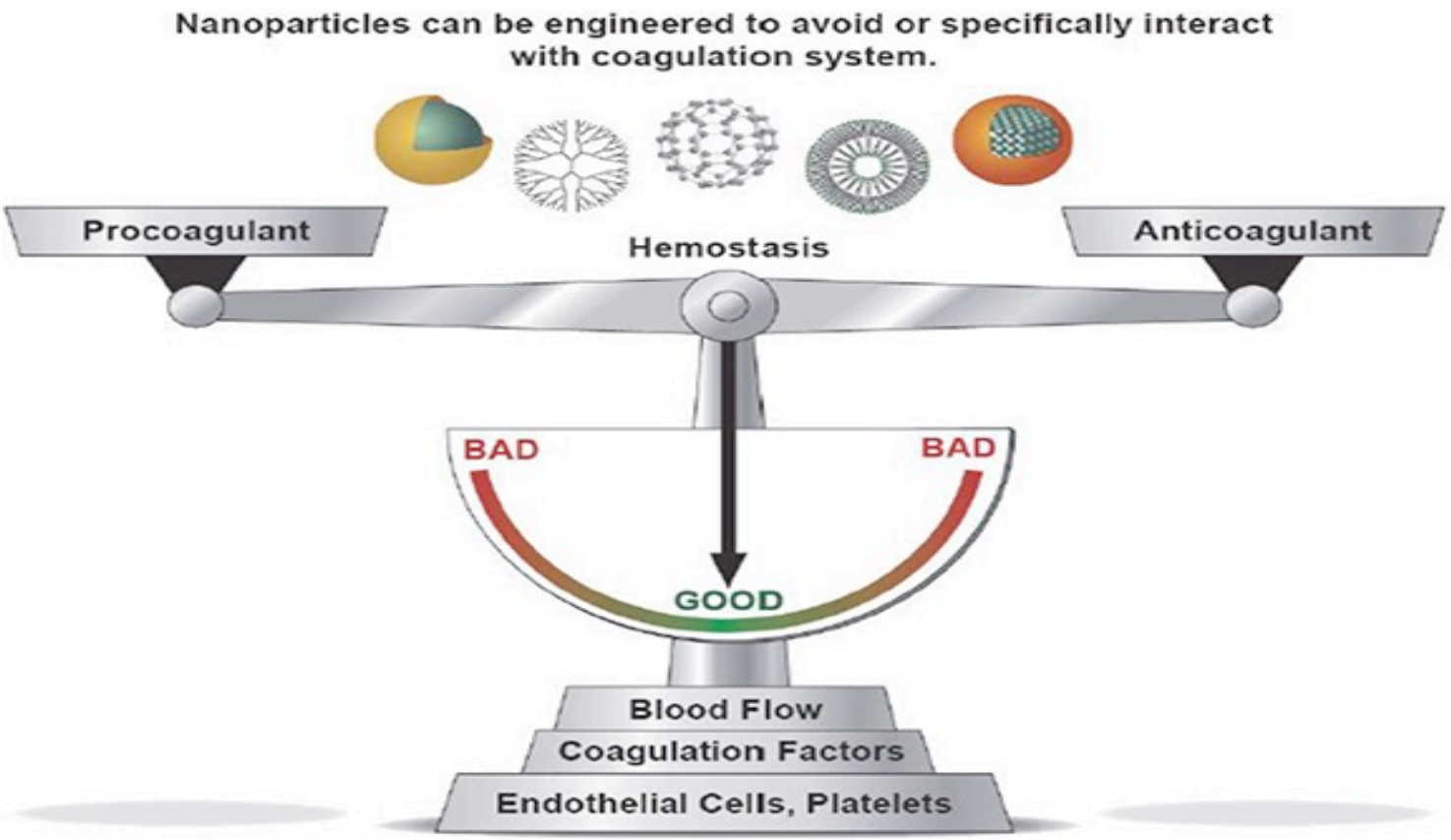
- Cationic dendrimers are more hemolytic than their anionic and neutral counterparts of the same size
- Larger dendrimers are more hemolytic than smaller

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

NCL data

Coagulation system

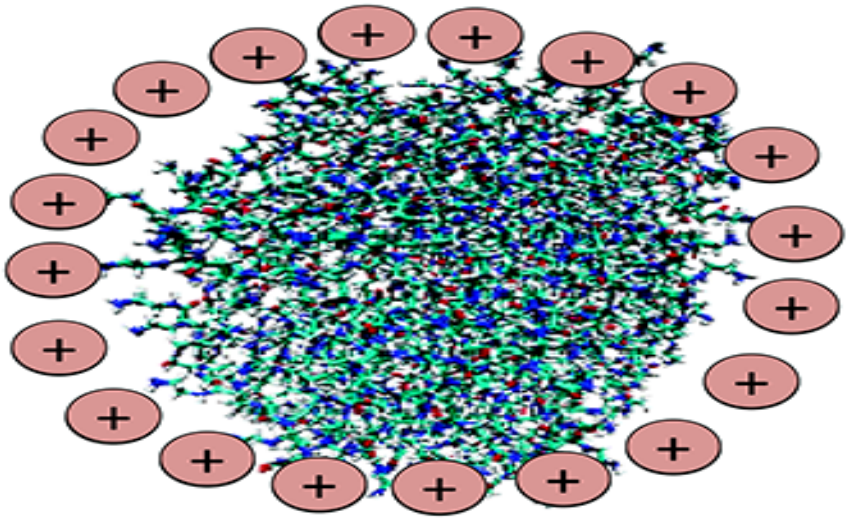
Coagulation system

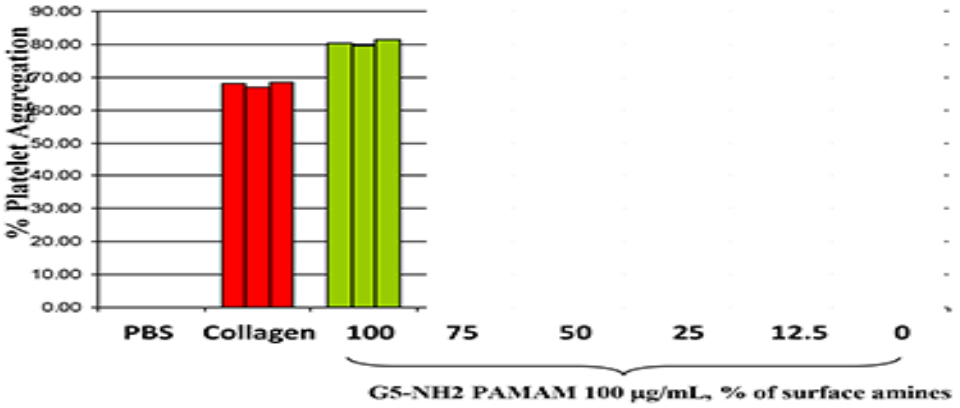


Ilinskaya A& Dobrovolskaia MA. Handbook of Immunological properties of Engineered Nanomaterials (2016), Vol 2

Zeta potential

Platelets: role of zeta potential





Zeta Potential is important
Less surface amines = less platelet aggregation

Infusion reactions

Infusion Reactions

- Infusion reactions (IRs) are the common Immune-mediated Adverse Effects of liposomal drugs
- Clinical signs of IR vary between patients and include one or more of the following symptoms: flushing, urticaria, rash, pruritus, shortness of breath, asthma, bronchospasm, apnea, hypotension, tachycardia, facial swelling, tightness in the chest and throat, headache, chills, chest pain, back pain, fever, cyanosis or syncope
- The more rapidly a reaction develops, the more severe it is likely to be

WARNINGS AND PRECAUTIONS

- Interstitial lung disease (ILD): Fatal ILD has occurred in patients receiving irinotecan HCl. Discontinue ONIVYDE if ILD is diagnosed. (5.1)
- Severe hypersensitivity reaction: Permanently discontinue ONIVYDE for severe hypersensitivity reactions. (5.4, 4)
- Embryo-fetal toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.5, 8.1, 8.3)

WARNING: CARDIOMYOPATHY and INFUSION-RELATED REACTIONS

See full prescribing information for complete boxed warning.

- **Myocardial damage may lead to congestive heart failure and may occur as the total cumulative dose of doxorubicin HCl approaches 550 mg/m². The risk of cardiomyopathy may be increased at lower cumulative doses with mediastinal irradiation (5.1).**
- **Acute infusion-related reactions occurred in 11% of patients with solid tumors. Serious, life-threatening, and fatal infusion reactions have been reported. Medications/emergency equipment to treat such reactions should be available for immediate use (5.2).**

VYXEOS may cause allergic reactions including anaphylaxis. Seek immediate medical attention if you develop signs and symptoms of anaphylaxis such as:

- trouble breathing
- severe itching
- skin rash or hives
- swelling of the face, lips, mouth, or tongue

WARNINGS

Anaphylaxis has been reported with amphotericin B deoxycholate and other amphotericin B-containing drugs, including AmBisome. If a severe anaphylactic reaction occurs, the infusion should be immediately discontinued and the patient should not receive further infusions of AmBisome.

Warnings

1. A triad of back pain, flushing, and chest tightness has been reported in 138% of the patients (16/116) treated with Daunoxome in the Phase III clinical trial, and in 2.7% of treatment cycles (27/994). This triad generally occurs during the first five minutes of the infusion, subsides with interruption of the infusion, and generally does not recur if the infusion is then resumed at a slower rate.

Infusion reactions

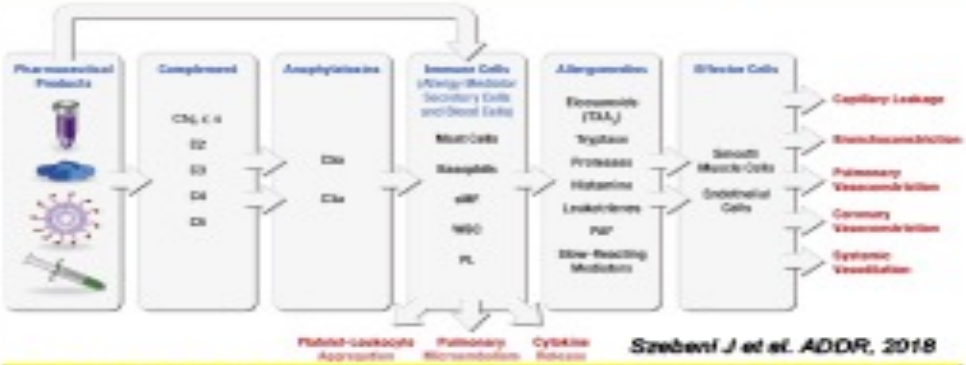
First Generation Liposomes & Infusion Reactions

NCL Alliance for Nanotechnology in Cancer

	Type I	Type II	Type III	Type IV
Underlying mechanism	Immediate hypersensitivity or acute allergy	Antibody-mediated cytotoxic reaction	Immune-complex-mediated reaction	Delayed-type hypersensitivity
Mediators	IgE	Cytotoxic IgM and IgG antibodies	Immune complexes (mostly IgM)	Mainly T-helper cells and macrophages. No antibodies involved
Immune response	Degranulation [Adaptive release] of mast cells and basophils and synthesis of new mediators [thromboxanes, prostaglandins and leukotrienes]	Cytotoxic actions by natural killer (NK) cells, macrophages, neutrophils and complement	Deposit of immune complexes in tissues, inflammatory response involving complement activation, reacting WBC degranulation and platelet activation	Cytotoxicity and accumulation of macrophages and T cells. Cytokine release and lymphocyte stimulation
Time to develop	Usually from minutes [15–30 minutes] to a few hours. Late-onset reactions [10–24 hours] are uncommon	From minutes to hours, but some clinical manifestations [thrombocytopenia, hemolytic anemia, fever, anaemia] can be diagnosed after a few days	From 3–8 hours, but some clinical manifestations can develop even 9–21 days after exposure	General [2–14] days
Clinical symptoms	Urticaria, angioedema, asthma, rhinitis, conjunctivitis, cardiorespiratory anaphylactic shock, bronchospasm	Hemolysis, nephritis, autoimmune haemolytic anaemia, thrombocytopenia, Goodpasture syndrome	Tissue injury. Several organs can be affected: lungs, joints, skin and kidneys. In addition, serum sickness, fever, glomerulonephritis, and vasculitis are possible	Mild cutaneous skin eruptions dependent on chemicals, cosmetics, drugs, and metals. Contact dermatitis, erythema, induration, maculopapular rash, and granuloma

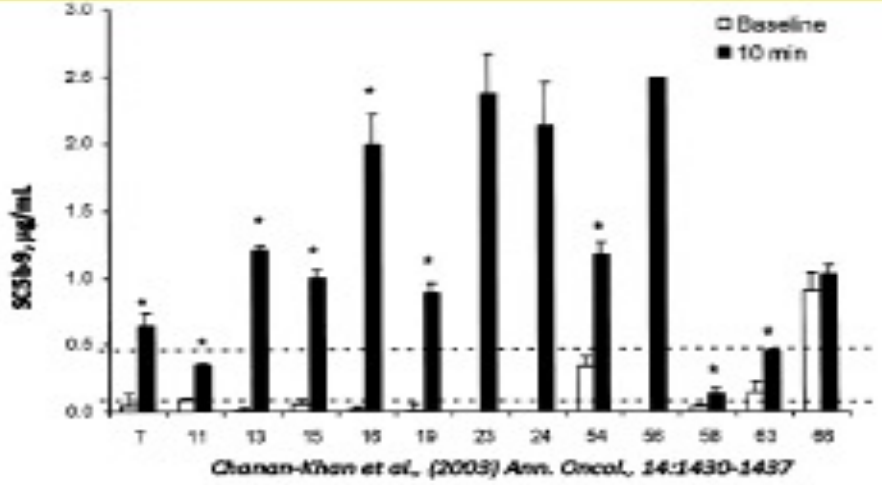
Szebeni J et al. Nature Nanotechnology, 2018

- 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



Szebeni J et al. ADDR, 2018

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



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

2nd generation liposomes

2nd Generation Liposomes Overcome Infusion Reactions

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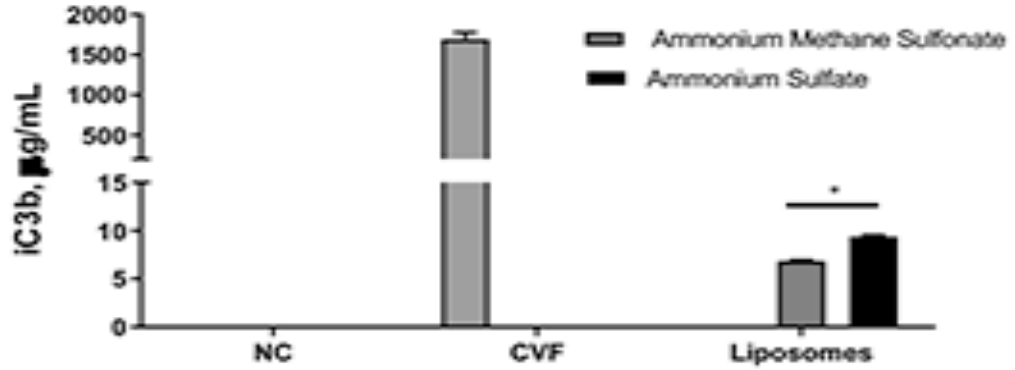
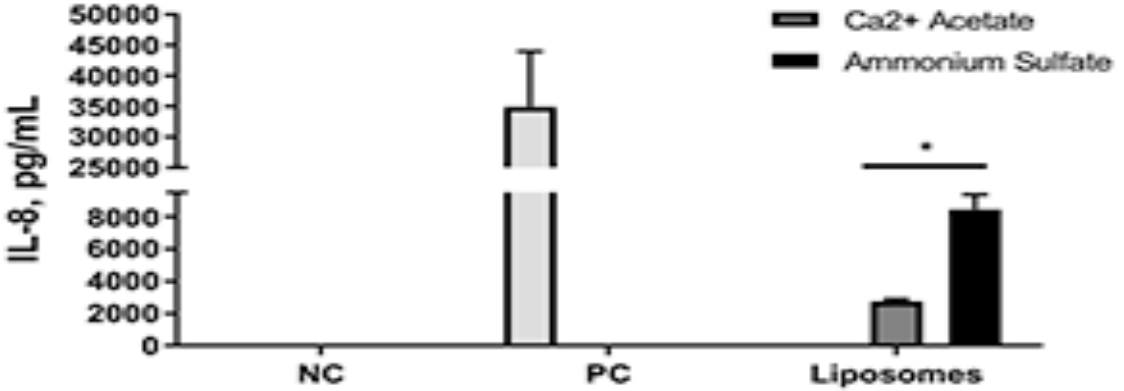
האוניברסיטה העברית בירושלים
THE HEBREW UNIVERSITY OF JERUSALEM

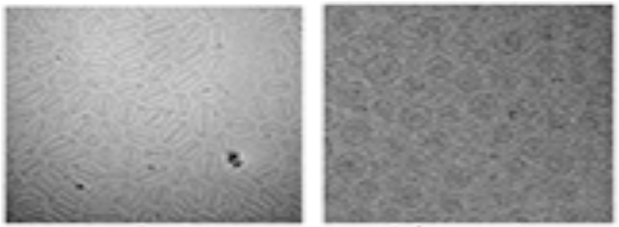
Difference in Biological Response



These data are generated in collaboration with Dr. Barenholz



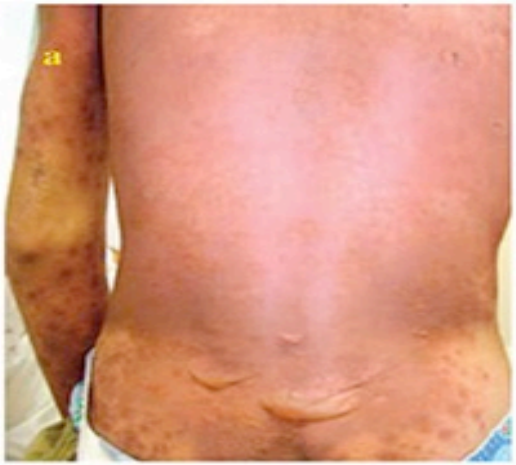
Difference in shape

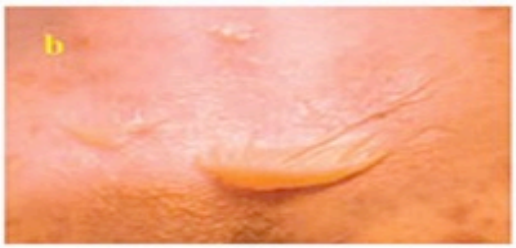


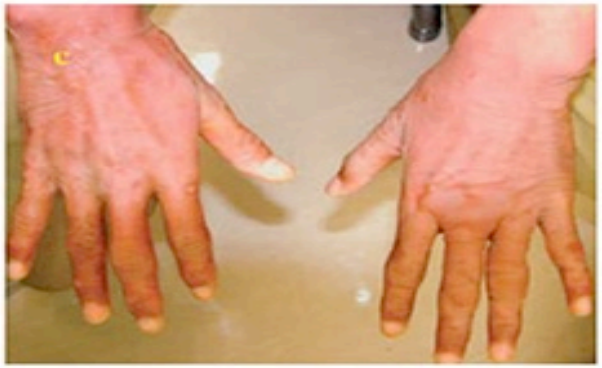
DOX=doxorubicin; NC= negative control; CVF= cobra venom factor; PEG = polyethylene glycol; PC = positive control

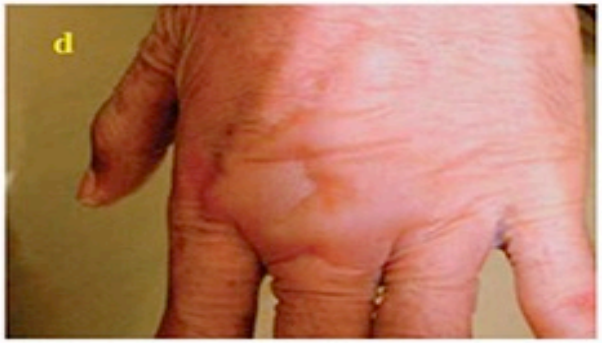
Allergenicity

Allergenicity: DTH to dendrimers









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

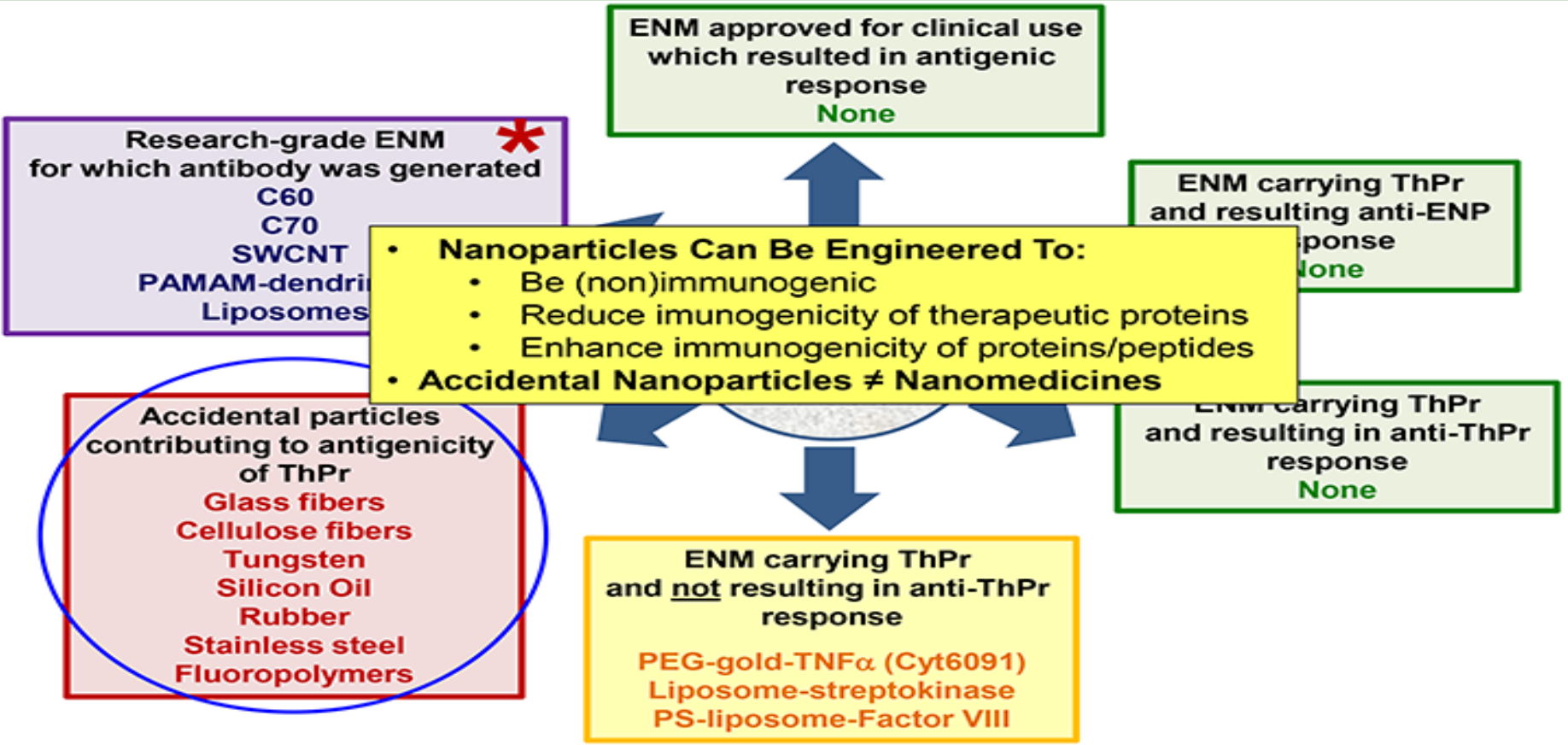
T. Toyama, H. Matsuda, I. Ishida, M. Tani, S. Kitaba, S. Sano and I. Katayama

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

- **Only one case of necrotizing dermatitis (type IV reaction) in response to dendrimers is reported in the literature: fever, chills, exudative erythema and fused bullae (Nikolsky's reaction)**
- **The mechanism is unknown**

Immunogenicity

Immunogenicity



* - 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

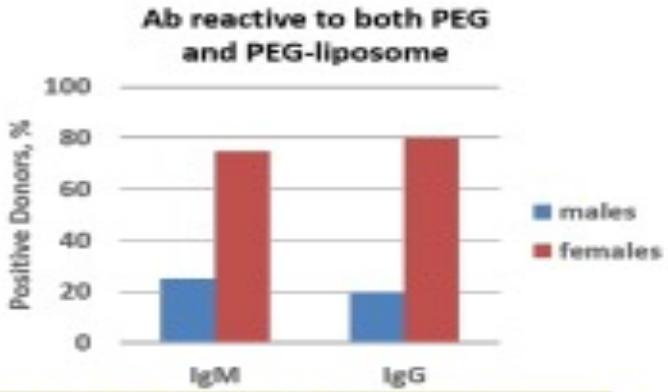
Dobrovolskaia & McNeil. *Handbook of Immunological properties of engineered nanomaterials*. WSP, 2013, ISBN 978-981-4390-25-5.

Anti-PEG antibody

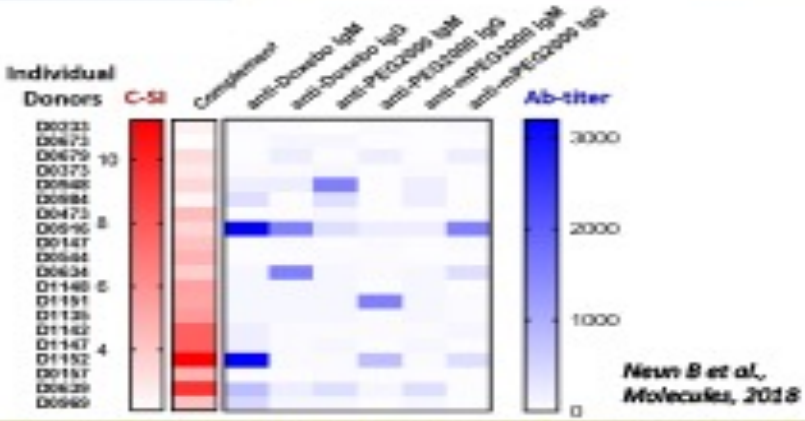
Pre-existing anti-PEG antibody

- 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



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-PEG antibodies

Anti-PEG antibodies and drug release

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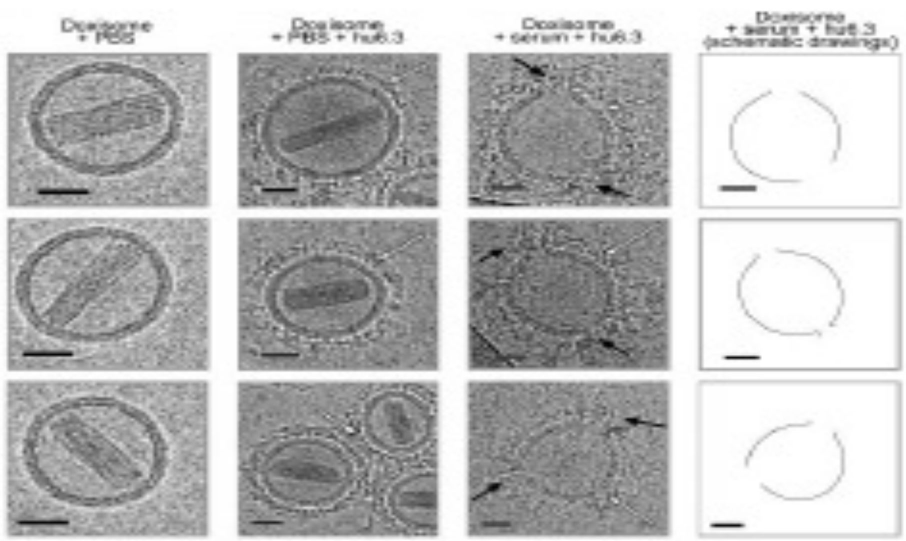
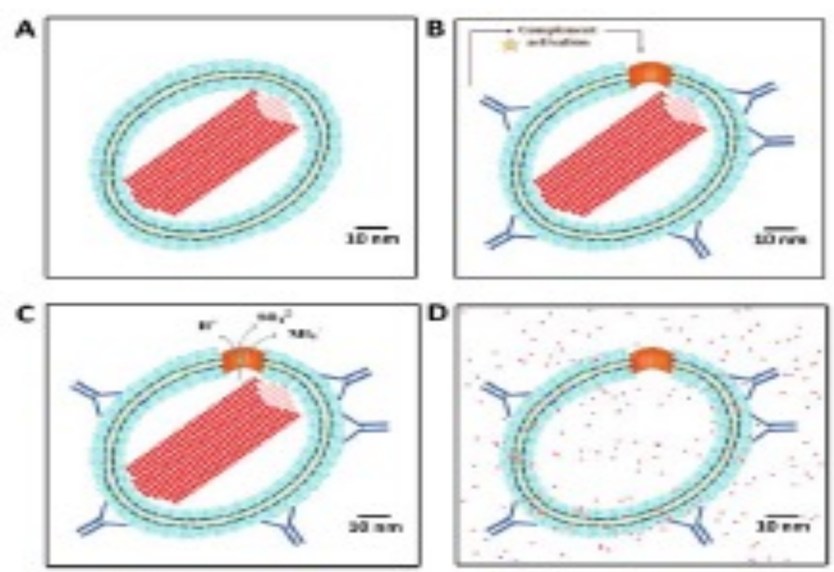
- Functional significance of these antibodies is incompletely understood
  - Triggering of premature drug release is one potential consequence



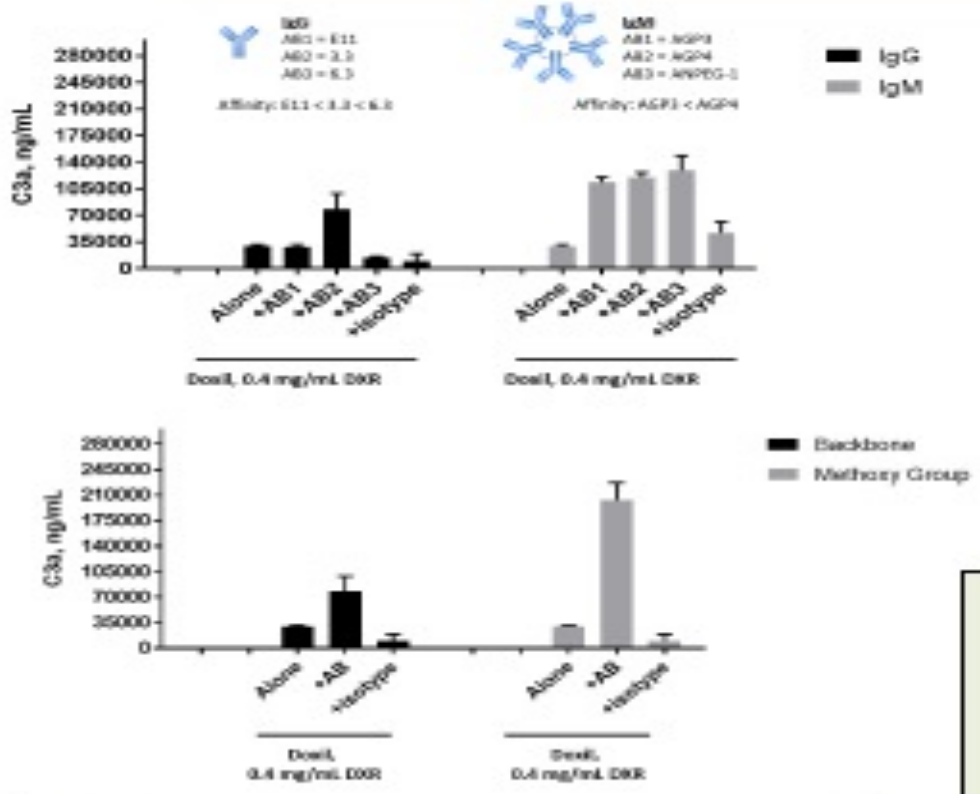


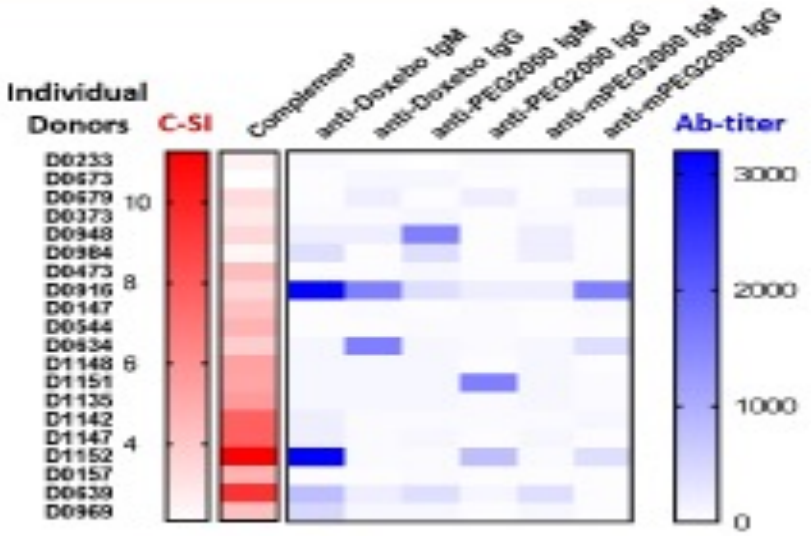
Chen E, Chen BM, Su YC, Chang YC, Cheng TL, Barenholz Y, Roffler SR. Premature Drug Release from Polyethylene Glycol (PEG)-Coated Liposomal Doxorubicin via Formation of the Membrane Attack Complex. ACS Nano. 2020 Jul 28;14(7):7808-7822. doi:10.1021/acsnano.9b07218. Epub 2020 Mar 6. PMID: 32142248.

Anti-PEG antibodies

Anti-PEG antibodies and CARPA

- Contribution to anaphylaxis has also been reported





- 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 assays identify toxicity
- Antibody screening helps identifying risk and understanding mechanisms

Purified anti-PEG antibodies contribute to the complement activation by Doxil

Anti-inflammatory properties

Anti-inflammatory and immunosuppressive properties

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Mechanism of Action

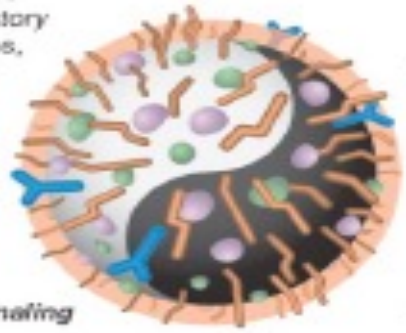
Anti-inflammatory

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

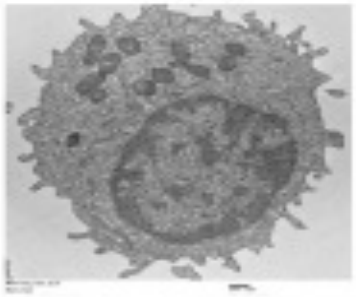
Direct

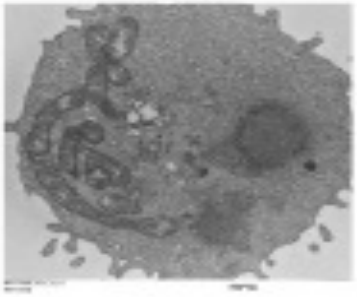
1. ***Inhibition of T-cell-mediated immunity***
   iron oxide NP, fullerene 60
2. ***Interference with functions of the cells of the immune system***
   iron oxide NP, PVA-SPION, MWCNT, quantum dots
3. ***Myelosuppression and toxicity to cells of the immune system***
   Sb_2O_3, Co, ZnO, TiO_2 NP

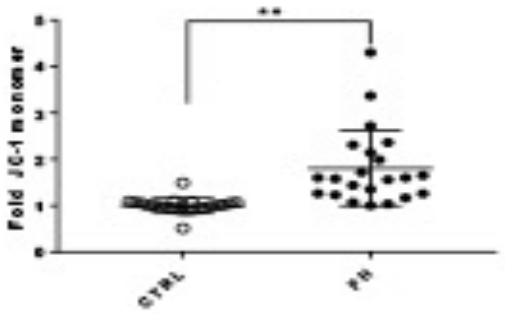
Mechanism of Action

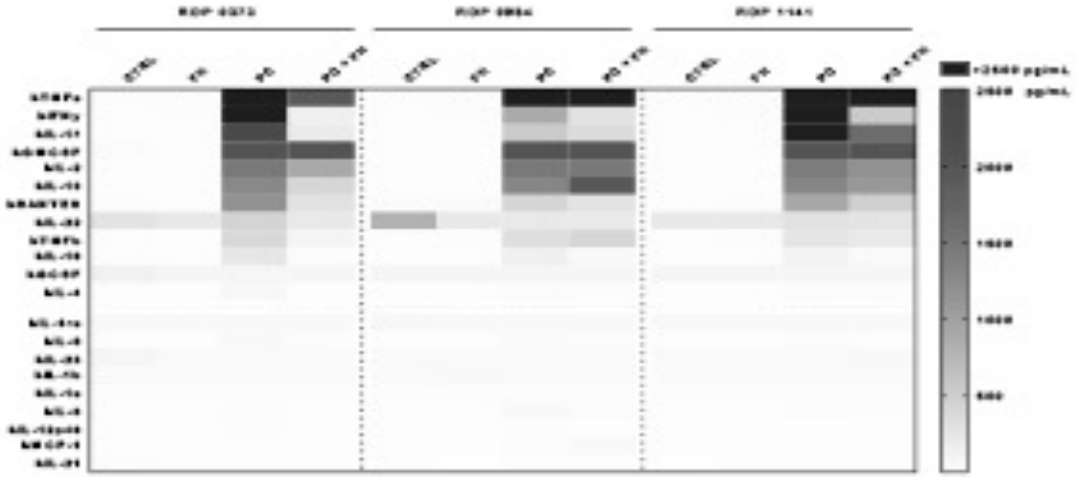
Immunosuppression

Immunosuppression



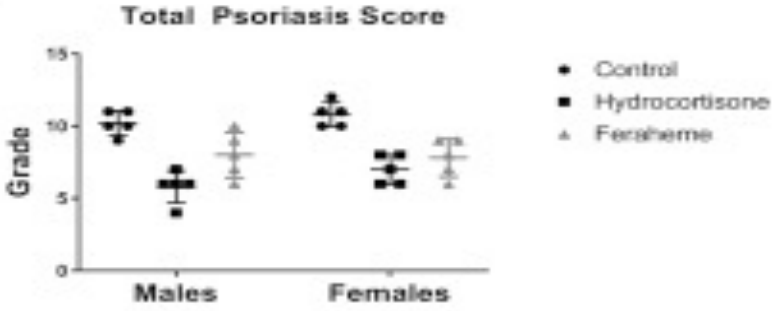






Iron oxide nanoparticles (Feraheme) suppresses activation of T-cells via a mechanism involving mitochondrial ROS in vitro

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

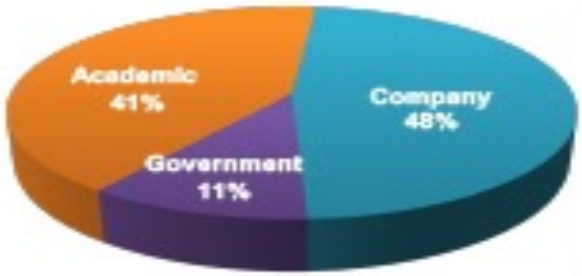
- Understanding SAR and mechanisms of toxicity can inform creation of safe and efficient complex drug systems

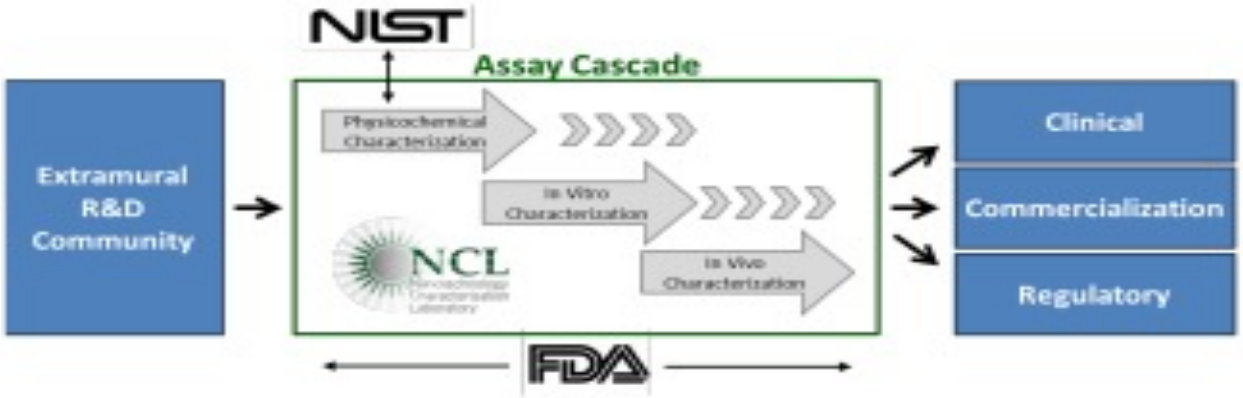
Nanotechnology characterization lab

Nanotechnology Characterization Lab

NCL Nanotechnology Characterization Laboratory | NCI Alliance for Nanotechnology in Cancer

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

NCL team

NCL Team

Frederick National Laboratory for Cancer Research

Funded by NCI Contract 75N91019D00024

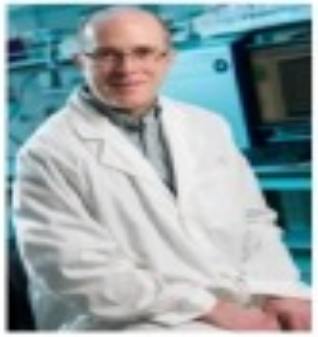
leidos Biomedical Research, Inc.

NCL immunology team

Special Thanks to the NCL Immunology Team

Current Members

Barry Neun



Edward Cedrone

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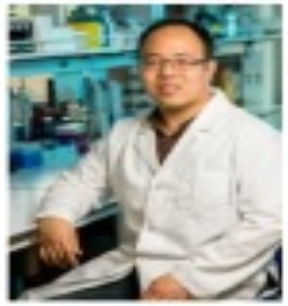
Jamie Rodriguez

Parag Aggarwal



Enping Hong

Ankit Shah