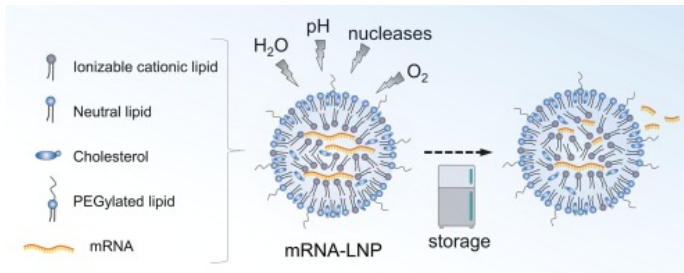


# Overlooked Biopharmaceutics of NanoMedicines / NanoVaccines Impacts Clinical Dose/Efficacy/Safety

**Duxin Sun, Ph.D.**

Charles Walgreen Jr. Professor of Pharmacy  
Professor of Pharmaceutical Sciences  
Director of Pharmacokinetics core  
Interdepartmental Program in Medicinal Chemistry  
Chemical Biology Program  
Comprehensive Cancer Center  
University of Michigan, Ann Arbor, MI 48109

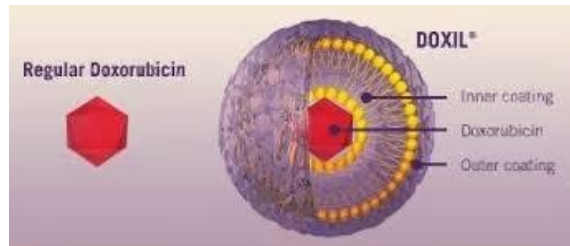
# Lipid Nanoparticle (LNP) of mRNA Vaccines is a Huge Success Against COVID19



S.C. injection for delivery to lymph nodes to induce B cell or T cell immunity against virus or cancer.

<https://www.sciencedirect.com/science/article/pii/S0378517321003914>

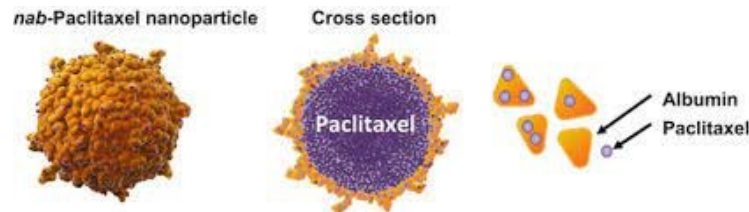
## Several Successful NanoMedicines for Cancer Treatment



<http://science-innovations.blogspot.com/2013/12/doxil-doxorubicin-hcl-liposome-injection.html>



<https://www.empr.com/drug/doxil/>



[https://link.springer.com/chapter/10.1007/978-981-10-2116-9\\_6](https://link.springer.com/chapter/10.1007/978-981-10-2116-9_6)



<https://www.indiamart.com/proddetail/abraxane-injections-8456427148.html>

Biopharmaceutics is very different

I.V. injection for delivery to tumors or other organs for kill cancer cells

# Different Biopharmaceutics for Oral Drug Products vs. NanoMedicines / NanoVaccines

- Biopharmaceutics for oral drug products
  - Physico-chemical properties, dosage forms
  - Impact oral absorption/bioavailability (plasma C<sub>max</sub>, T<sub>max</sub>, AUC) (PO)
  - Sameness of plasma PK profiles ensure the sameness of clinical dose/efficacy/toxicity
- Biopharmaceutics for Nanomedicines / NanoVaccines
  - Physico-chemical properties, nanoformulations
  - Impact drug exposure and localizations of NanoMedicines in disease targeted tissues vs. in normal tissues vs. in plasma (IV injection)
  - Impact exposure and localization of nanovaccines in lymph nodes vs. other tissues vs. in plasma (SC injection)
  - Consequently, alter clinical dose/efficacy/toxicity

# Implication of Biopharmaceutics of NanoMedicines / NanoVaccines

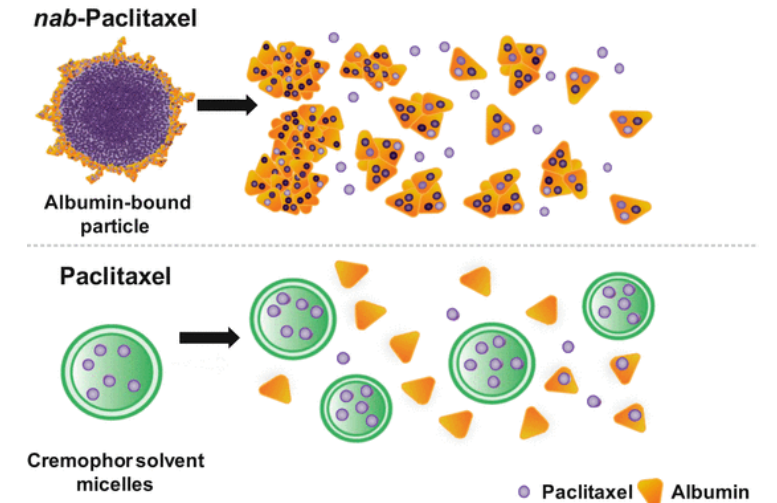
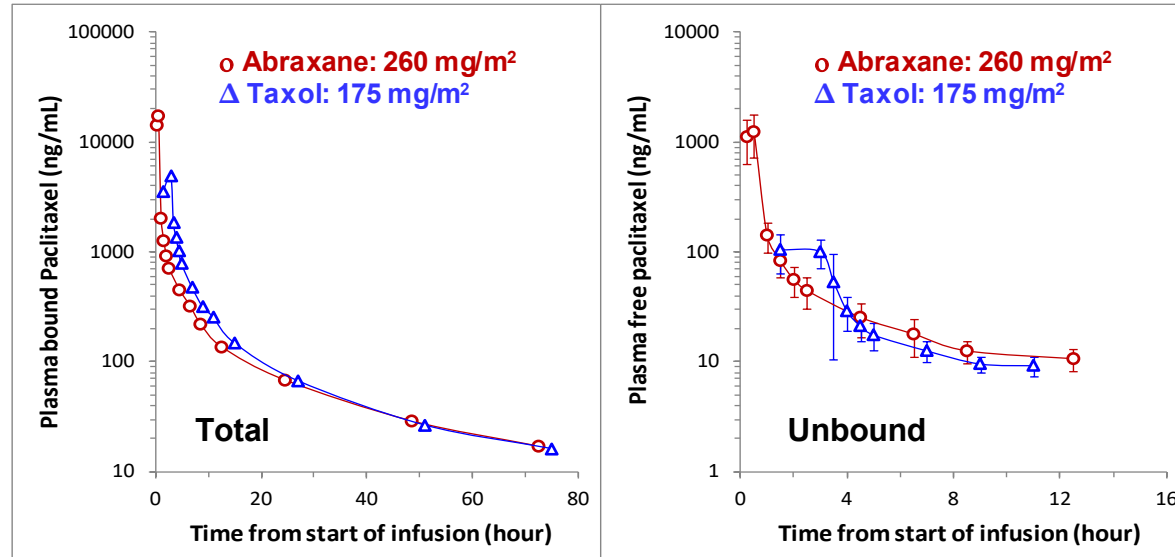
- Ensure Product Quality
  - What are the product quality attributes to be controlled?
  - What are the specifications of the products? Why?
- Regulatory approval
  - 505(b)(2) pathway?
    - Based on plasma profile?
    - Based on tissue profiles? What tissue profiles? How to monitor??
  - What data need to be submitted for products approval?
- Design and Development Criteria
  - NanoMedicine design criteria?
  - NanoVaccine design criteria?

# I. Could 505(b)(2) Pathway be Used for Different NanoMedicines (IV Injection)?

Based on Plasma Exposure?

Based on Tissue Exposure/Localization?

# Could be 505(b)(2) Pathway be Used for Abraxane vs. Taxol Based on Plasma Exposure (IV Injection)?

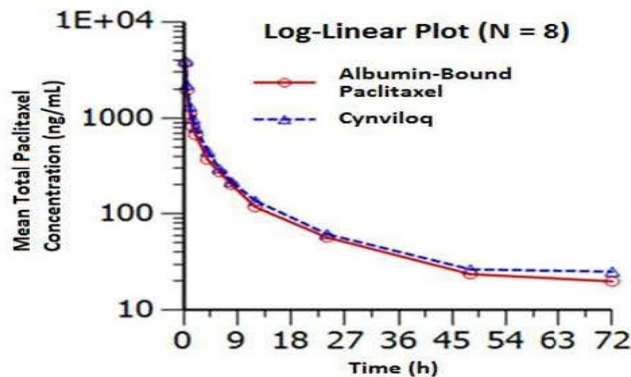


[https://link.springer.com/chapter/10.1007/978-981-10-2116-9\\_6](https://link.springer.com/chapter/10.1007/978-981-10-2116-9_6)

PK Parameter	Abraxane (260 mg/m <sup>2</sup> ), 0.5 h IV		Taxol (175 mg/m <sup>2</sup> ), 3 h IV	
	N	Mean (CV%)	N	Mean (CV%)
CL (L/h/m <sup>2</sup> )	56	18.3 (26.0)	38	12.9 (37.8)
Fu (%)	14	6.3 (33.3)	14	2.4 (37.5)
<b>Total AUC (h*ng/mL)</b>	<b>56</b>	<b>20324</b>	<b>38</b>	<b>20821</b>
Total C <sub>max</sub> (ng/mL)	14	19556	14	5128

# Could be 505(b)(2) Pathway be Used for Abraxane vs. Cynviloq (genexol-PM) vs. Apealea Based on Plasma exposure (IV Injection)?

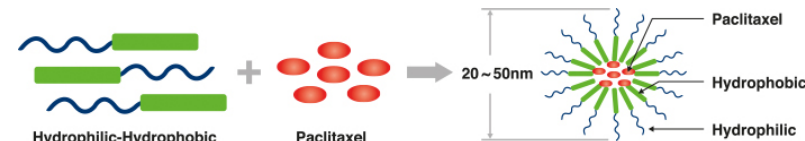
## Initial PK Data Analyses Suggest BE vs. Albumin-Bound Paclitaxel



BE Assessment and Sample Size Estimate

Parameters	Ratio of Cynviloq/ Albumin-bound paclitaxel (%)	90% CI
$\ln(AUC_{0 \text{ to } \infty})$	109.1	93.98 – 126.58
$\ln(C_{\text{max}})$	102.5	83.10 – 126.35
Point estimate $110 - \ln(AUC_{0 \text{ to } \infty})$	N = 53 with 90% power	

## Cynviloq (Genexol-PM) PEG-PLA nanoparticle (micelle)



<https://samyangbiopharm.com/eng/ProductIntroduce/injection01>

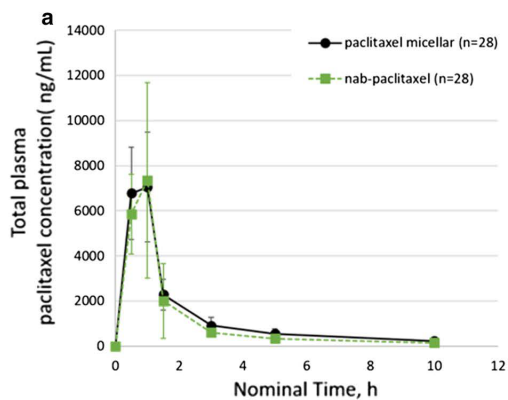


Fig. 2 Mean ( $\pm$  SD) in all patients of total paclitaxel concentration micellar or nab-paclitaxel, 260 mg/m<sup>2</sup>, plotted in a line graph.

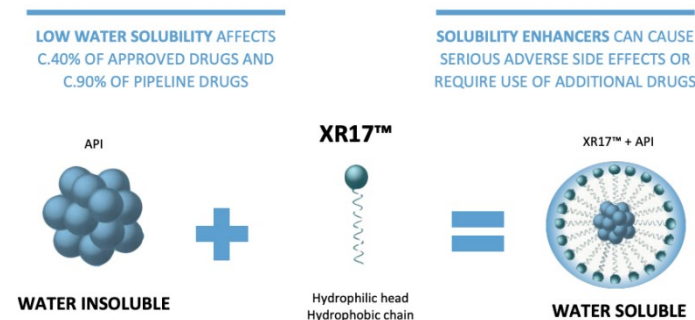
Table 3 Bioequivalence (BE) analyses of comparison of various PK parameters of total and unbound plasma concentrations of paclitaxel micellar with nab-paclitaxel

PK parameter	Formulation log scale point estimate (90% CI)			BE comparison point estimate (90% CI)
	Nab-paclitaxel	Paclitaxel micellar	Nab-paclitaxel/paclitaxel micellar	
<b>Total paclitaxel</b>				
$AUC_{0-10h}$ (h*ng/ml)	9.31 (9.23:9.39)	9.48 (9.39:9.56)	- 0.17 (- 0.27:- 0.07)	0.85 (0.76:0.94)
$C_{\text{max}}$ (ng/ml)	8.91 (8.80:9.01)	8.97 (8.86:9.07)	- 0.06 (- 0.20:0.08)	0.94 (0.82:1.09) <sup>BE</sup>
<b>Unbound paclitaxel</b>				
$AUC_{0-10h, u}$ (h*ng/ml)	6.33 (6.24:6.41)	6.44 (6.36:6.53)	- 0.12 (- 0.22:- 0.01)	0.89 (0.80:0.99) <sup>BE</sup>
$C_{\text{max}, u}$ (ng/ml)	5.93 (5.83:6.04)	5.95 (5.85:6.06)	- 0.02 (- 0.16:0.12)	0.98 (0.86:1.12) <sup>BE</sup>
<b>Ratio</b>				
$f_u^a$	- 0.75 (- 0.80:- 0.71)	- 0.82 (- 0.86:- 0.77)	0.06 (0.01:0.12)	1.07 (1.01:1.12) <sup>BE</sup>

CI confidence interval, BE indicates that bioequivalence is shown

<sup>a</sup> Test parameter  $AUC_{0-10h}$  of the  $f_u$ -time curve; unit hours

## Apealea (Paclical) XR-17 nanoparticle (micelle)



<https://www.edisongroup.com/publication/an-appealing-metamorphosis/27693/>

# The Unique Clinical Efficacy/Safety of Different Anticancer NanoMedicines

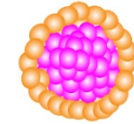
- Abraxane (Albumin nanoparticle) vs. Taxol

- Efficacy

- Superior efficacy in breast cancer vs. Taxol
- Superior efficacy in non-small cell lung cancer (Abraxane + carboplatin vs. Taxol + carboplatin) Superior efficacy in pancreatic cancer (abraxane + gemcitabine vs. gemcitabine)
- No efficacy difference in gastric cancer vs. Taxol

- Adverse Events

- Less neutropenia
- More neuropathy,
- More GI toxicity



Abraxane  
≈136 nm

- Genexol-PM (PEG-PLA nanoparticle) vs. Taxol

- Efficacy

- Non-inferior efficacy in metastatic breast cancer

- Adverse Events

- Increased neutropenia



Genexol-PM  
≈22 nm

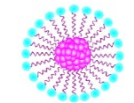
- Paclical (all-trans retinoic acid analog micelle) vs. Taxol

- Efficacy

- Non-inferior efficacy in ovarian cancer

- Adverse Events

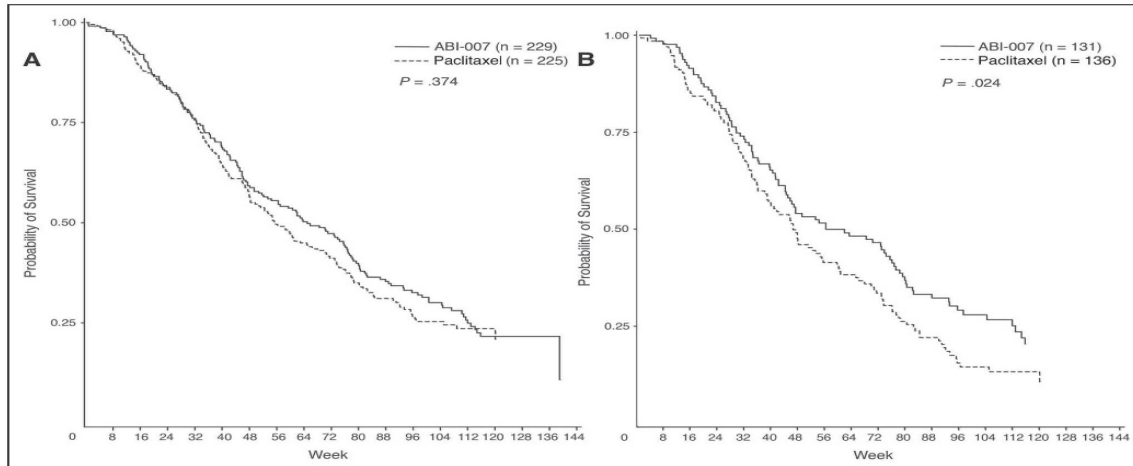
- Not sure?



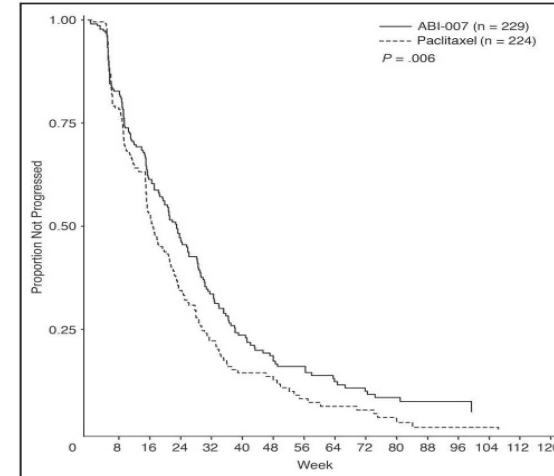
Paclical  
≈42 nm



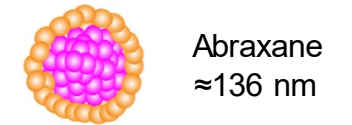
# Abraxane Showed Superior Efficacy vs. Taxol Genexol-PM Showed Non-inferior Efficacy vs. Taxol in Breast Cancer Patients



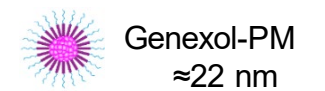
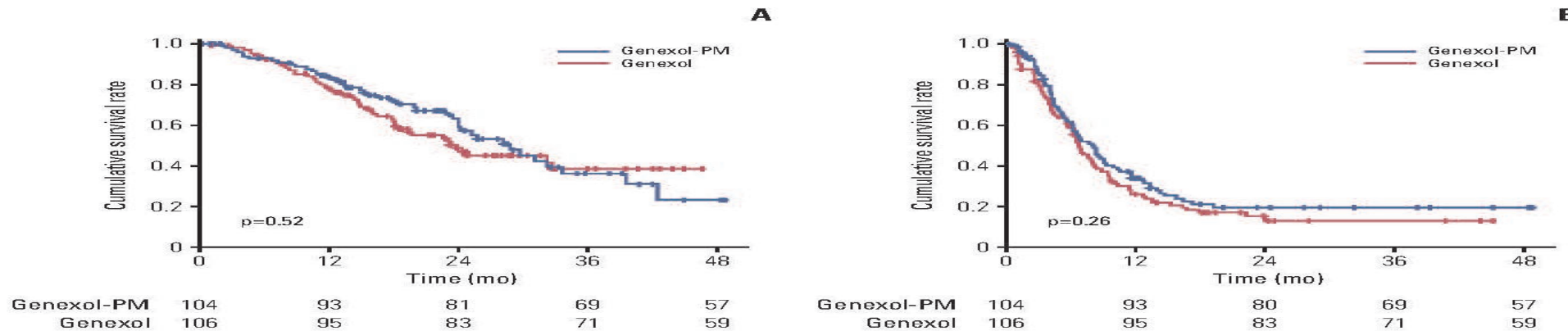
**Fig 2.** (A) Patient survival over time. (B) Patient survival over time in patients who received second-line or greater therapy. P values from log-rank test. Survival indicates time from first dose of study drug to date of death.



**Fig 1.** Median time to disease progression.



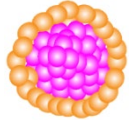
J Clin Oncol 23(31) (2005) 7794-803



**Fig. 3.** Survival analysis according to treatment. (A) Overall survival. (B) Progression-free survival.

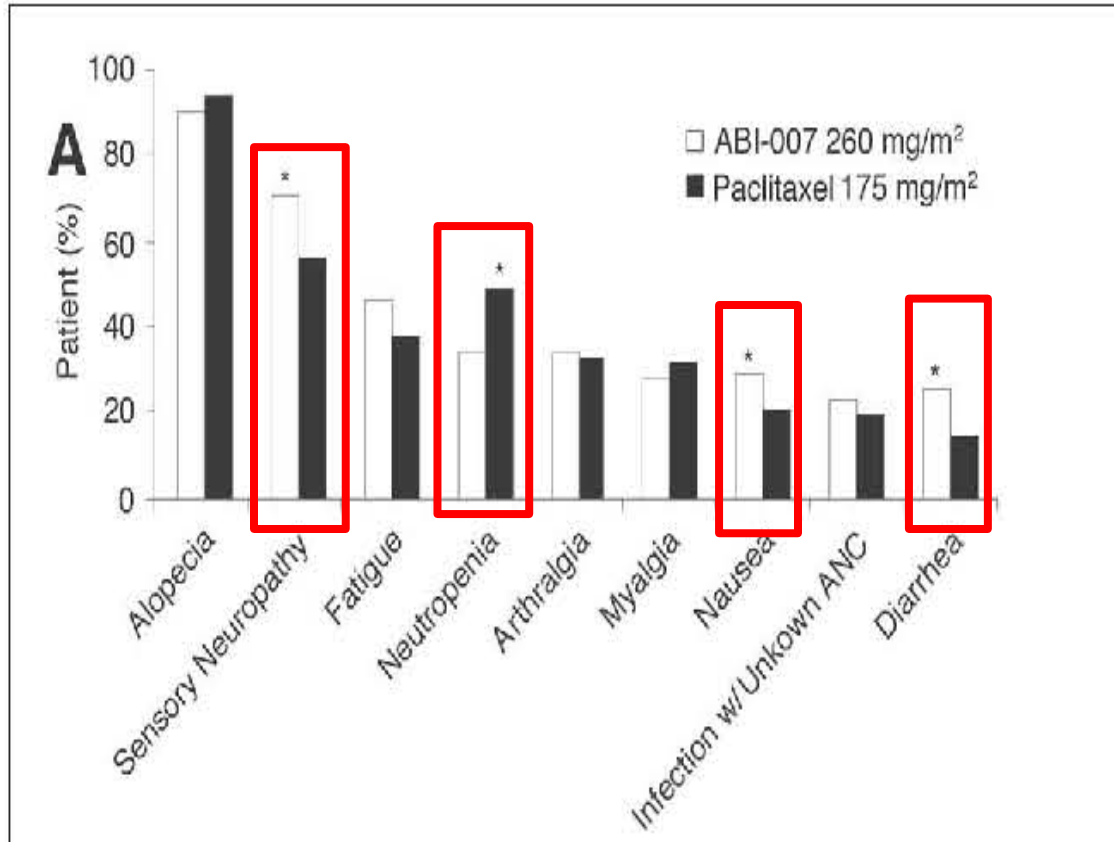
Cancer Res Treat 49(3) (2017) 569-577.

# Abraxane and Genexol-PM Have Distinct Adverse Events (AEs) vs. Taxol



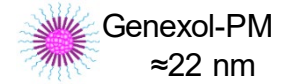
Abraxane  
≈136 nm

## Abraxane vs. Taxol



J Clin Oncol 23(31) (2005) 7794-803

## Genexol-PM vs. Taxol



Genexol-PM  
≈22 nm

Table 4. Adverse events

Adverse event	Genexol-PM (n=105)			Genexol (n=107)		
	Grade 1	Grade 2	≥ Grade 3	Grade 1	Grade 2	≥ Grade 3
Neutropenia	0	3 (2.9)	72 (68.6)	0	8 (7.5)	43 (40.2)
Febrile neutropenia	0	1 (1.0)	3 (2.9)	0	0	3 (2.8)
Myalgia	26 (24.8)	28 (26.7)	9 (8.6)	32 (29.9)	26 (24.3)	8 (7.5)
Nausea	25 (23.8)	14 (13.3)	3 (2.9)	42 (39.3)	6 (5.6)	1 (0.9)
Neuropathy peripheral	13 (12.4)	16 (15.2)	8 (7.6)	27 (25.2)	14 (13.1)	8 (7.5)
Constipation	17 (16.2)	22 (21.0)	0	23 (21.5)	17 (15.9)	0
Arthralgia	11 (10.5)	12 (11.4)	1 (1.0)	9 (8.4)	14 (13.1)	3 (2.8)
Asthenia	8 (7.6)	4 (3.8)	4 (3.8)	14 (13.1)	11 (10.3)	1 (0.9)
Rash	16 (15.2)	11 (10.5)	2 (1.9)	12 (11.2)	9 (8.4)	4 (3.8)
Pruritus	13 (12.4)	9 (8.6)	0	17 (15.9)	8 (7.5)	0
Insomnia	13 (12.4)	7 (6.7)	1 (1.0)	10 (9.3)	7 (6.5)	0
Hypersensitivity	5 (4.8)	8 (7.6)	3 (2.9)	2 (1.9)	1 (0.9)	1 (0.9)

Values are presented as number (%).

Cancer Res Treat 49(3) (2017) 569-577.

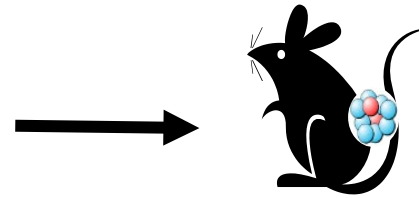
## II. What Went Wrong with Anticancer NanoMedicine Design

# Current Anticancer NanoMedicine Design Criteria

## Universal NanoDelivery Platform

- ❖ Tumor accumulation by Enhanced Permeability Retention (EPR) to improve efficacy
- ❖ Long circulation and high plasma concentration to reduce normal organ accumulation, reduce toxicity
- ❖ One universal nanodelivery platform for different drugs

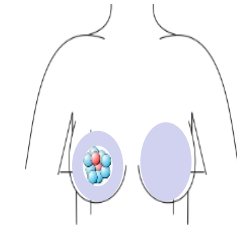
## Preclinical Evaluation Enhanced Delivery Efficiency and Anticancer Efficacy



Subcutaneous Cancer

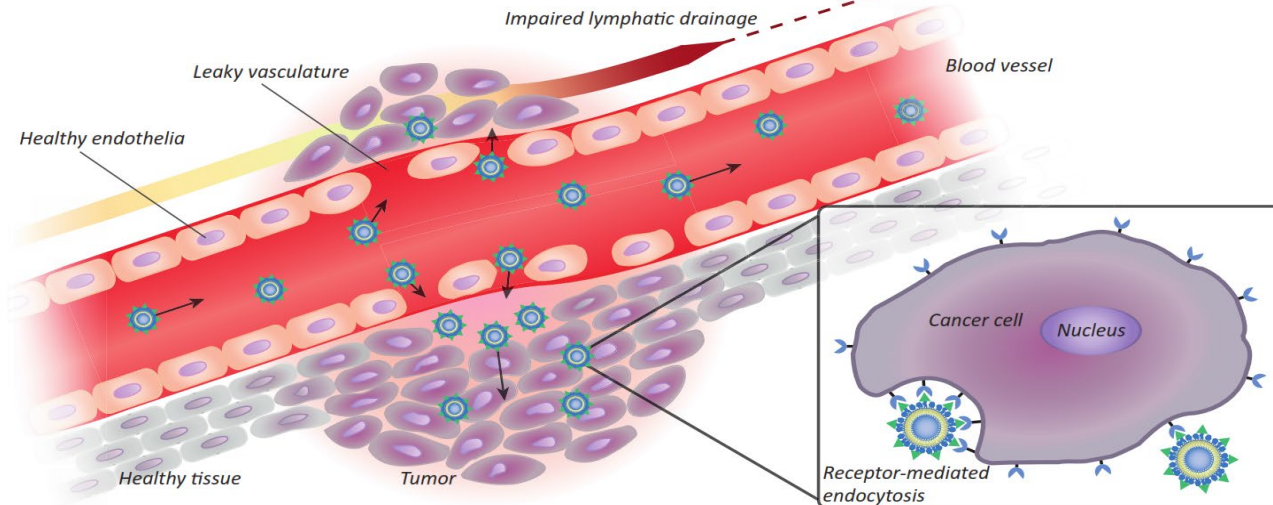


## Clinical Translation Altered Efficacy and Adverse Events

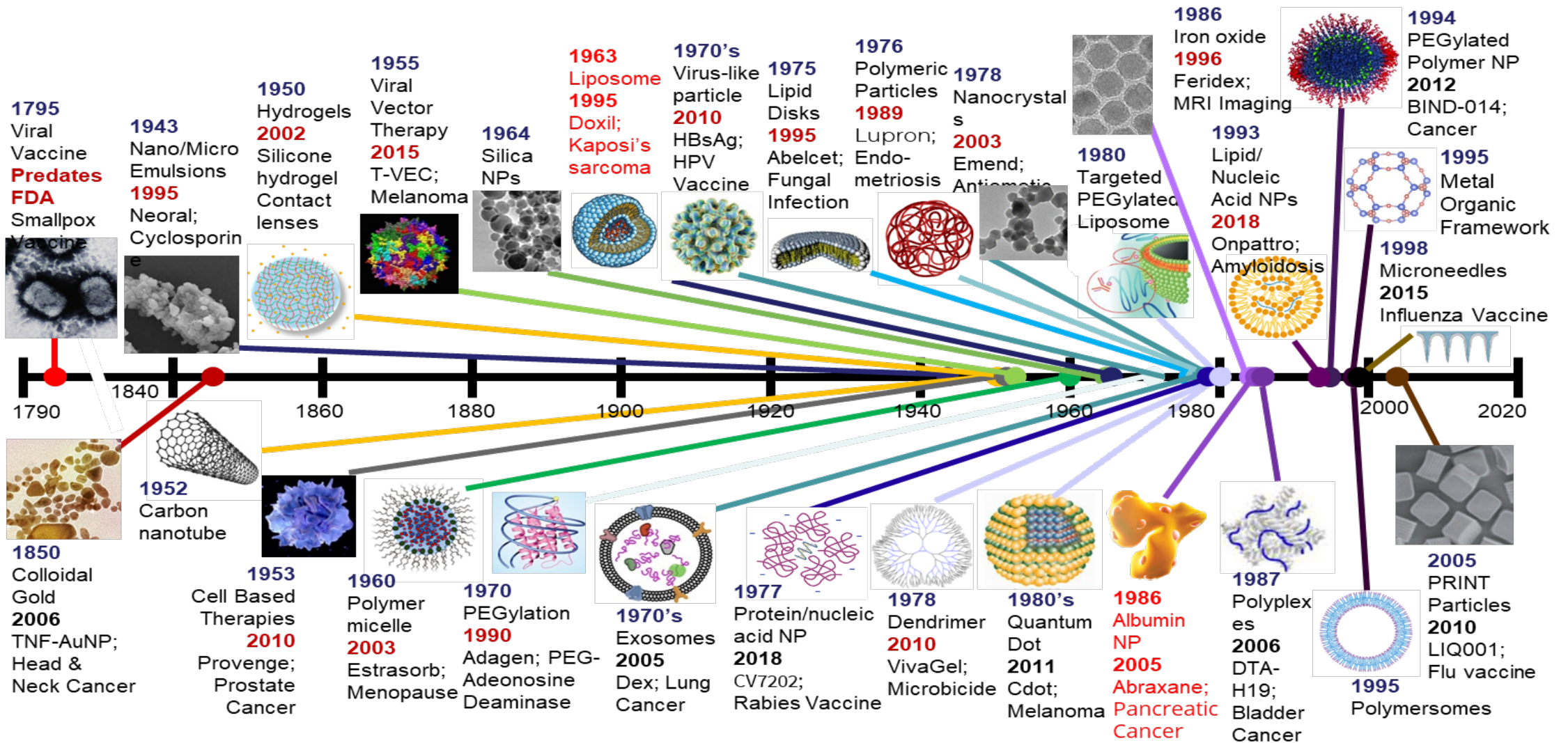


Cancer Patients

Sun, D et al. ACS Nano, 2020, 14: 12281-12290  
Luan, and Sun et al. Biomaterial, 2021, 275: 120910



# Micro-, Nano-Technology for Therapeutic, Vaccine, and Imaging



All images from Google images

Green: Date of 1st report of technology, not just for drug delivery | Yellow: Date of 1st Clinical Trial if not approved | Red: Date of FDA approval | NP = nanoparticle

@AinslieLab UNC

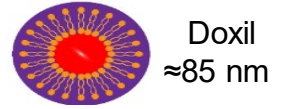
# **Inconsistency in Nanomedicines' Efficacy/Safety**

## Between Preclinical Cancer Models and Human Cancer Patients.

- Most anticancer nanomedicines failed in clinical trials, despite excellent efficacy in preclinical cancer xenograft models
- Many successful anticancer nanomedicines were approved by comparison between nanomedicines + standard care vs. standard care alone, without comparison with free drugs
- The clinical efficacy/safety of successful anticancer nanomedicines, in comparison with free drugs, are inconsistent with current nanomedicine design criteria
- NanoMedicine did not universally decrease toxicity, but alter toxicity profiles

# The Clinical Efficacy/Safety of Anticancer NanoMedicines are Inconsistent with NanoMedicine Design Criteria

- Doxil (PEGylated liposome) vs. doxorubicin



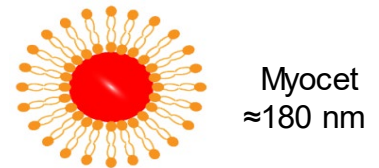
- Efficacy

- Superior efficacy in AIDS related Kaposi's sarcoma vs. ABV
- No difference in metastatic breast cancer vs. doxorubicin
- No difference in ovarian cancer vs. topotecan
- Better efficacy in multiple myeloma (Doxil + Bortezomib vs. Bortezomib)

- Adverse Events

- Reduced cardiotoxicity (myopathy)
- Increased hand-and-foot syndrome (PPE), rash, mucositis, abdominal pain, pigmentation, erythema

- Myocet (Un-PEGylated liposome) vs. doxorubicin



- Efficacy

- No difference in metastatic breast cancer (Myocet+ cyclophosphamide vs. doxorubicin + cyclophosphamide)

- Adverse Events

- Reduced cardiotoxicity (myopathy), neutropenia, stomatitis
- Only one report for hand foot syndrome (PPE)

# The Clinical Efficacy/Safety of Anticancer NanoMedicines are Inconsistent with NanoMedicine Design Criteria

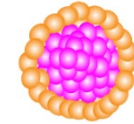
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- Superior efficacy in breast cancer vs. Taxol
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- No efficacy difference in gastric cancer vs. Taxol

- Adverse Events

- Less neutropenia
- More neuropathy,
- More GI toxicity



Abraxane  
≈136 nm

- Genexol-PM (PEG-PLA nanoparticle) vs. Taxol

- Efficacy

- Non-inferior efficacy in metastatic breast cancer

- Adverse Events

- Increased neutropenia



Genexol-PM  
≈22 nm

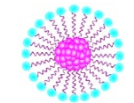
- Paclical (all-trans retinoic acid analog micelle) vs. Taxol

- Efficacy

- Non-inferior efficacy in ovarian cancer

- Adverse Events

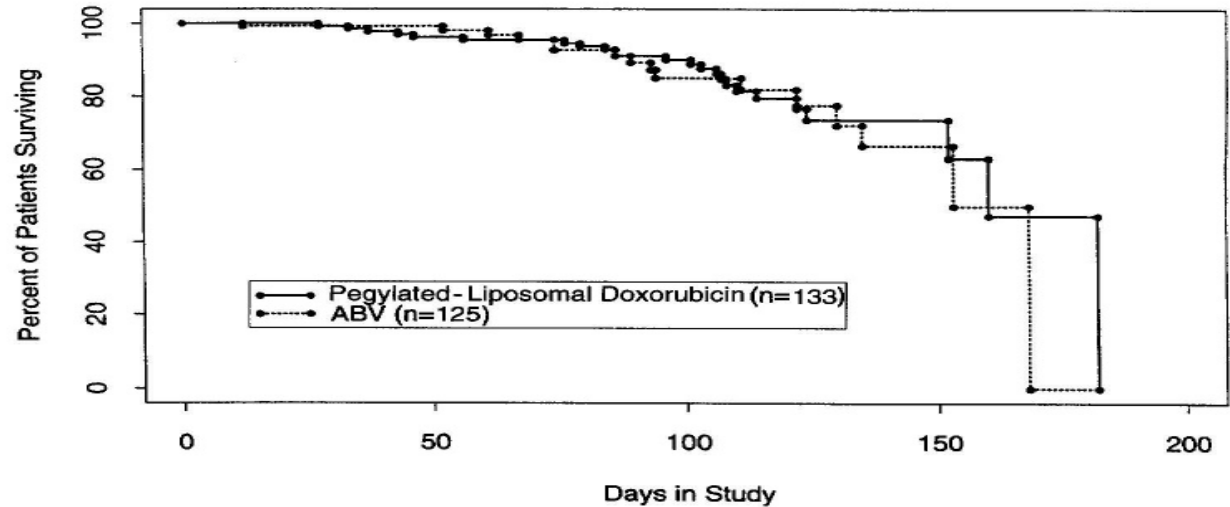
- Not sure?



Paclical  
≈42 nm



# Doxil Showed Superior Efficacy vs. ABV in AIDS-related Kaposi's Sarcoma, but Similar Efficacy to Doxorubicin in Breast Cancer Patients



AIDS-related sarcoma

J Clin Oncol 16(7)  
(1998) 2445-51

Breast Cancer

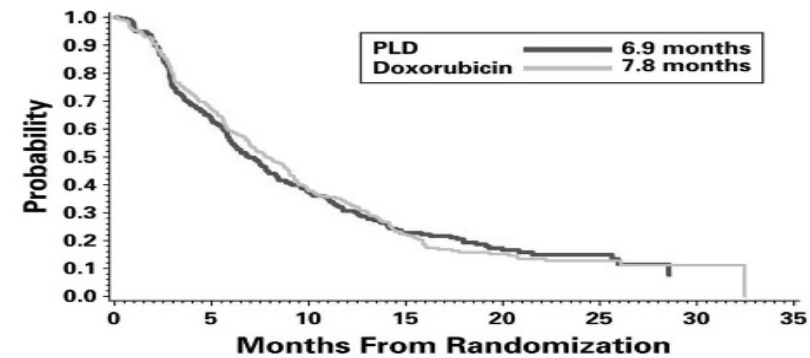
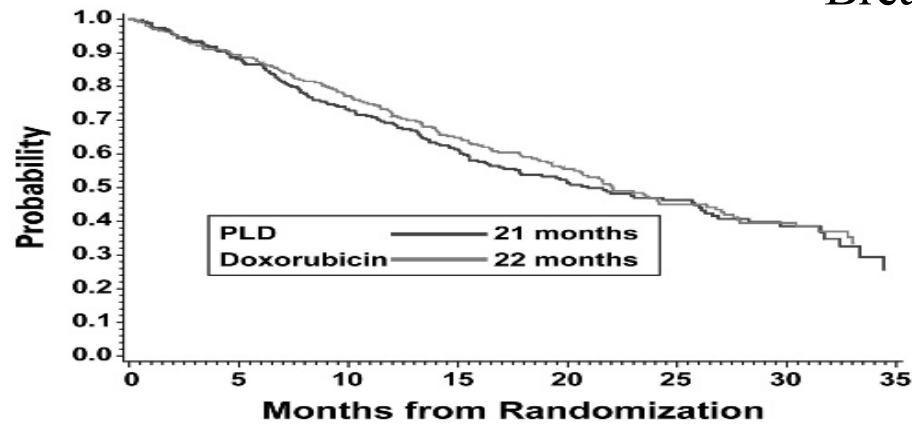


Figure 4. Overall survival [HR = 0.94 (95% CI for HR 0.74–1.19)].

Figure 1. Progression-free survival [HR = 1.00 (95% CI for HR 0.82–2.2)].

# What Went Wrong with Anticancer NanoMedicine Design

For every complex problem  
there is an answer that is  
**clear, simple, and wrong**

[H.L. Mencken]



**Henry Louis Mencken, 9/12/1880 – 01/29/1956**

American journalist, essayist, satirist, cultural critic, and scholar of American English

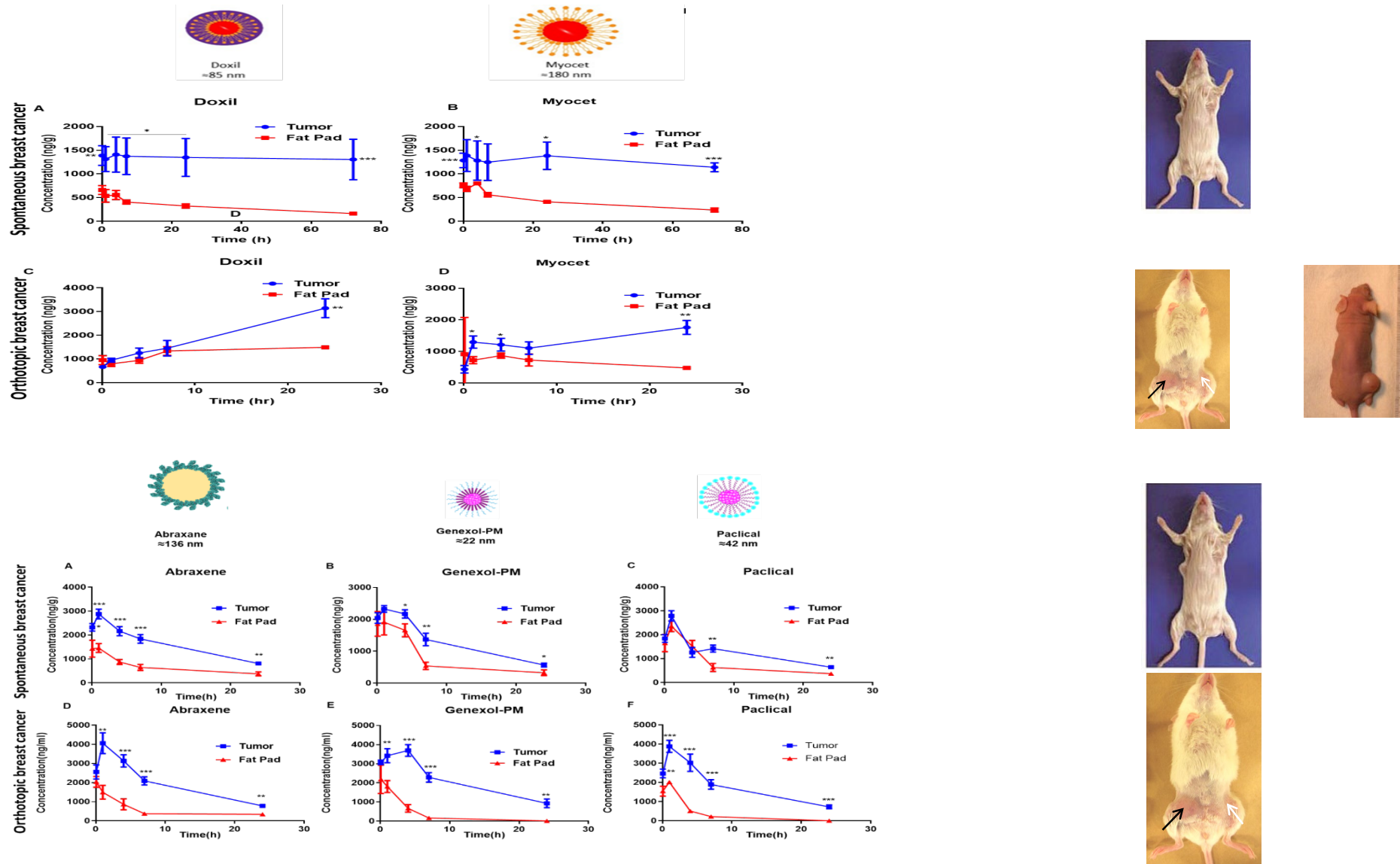
**Nanomedicine Design Only Based on Tumor Enhanced  
Permeability and Retention (EPR)**

**May Not Be the Right Strategy in Human Cancer Patients.**

## **Debate on Nanomedicine Design Based on Tumor EPR May Have Mixed Two Different Questions**

- Does tumor EPR exist in mouse xenograft cancers and human cancers in comparison with normal tissues?
- Can nanomedicines enhance drug accumulation in tumors by EPR, in comparison with free drugs, to improve clinical anticancer efficacy?

# Tumor EPR Was Observed for NanoMedicines breast tumors vs. normal breast tissues



# Tumor EPR was Observed for NanoMedicines in Human Cancers vs. Normal Tissues

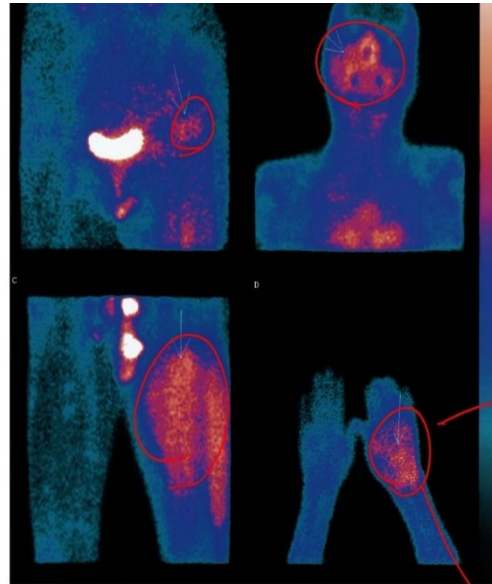
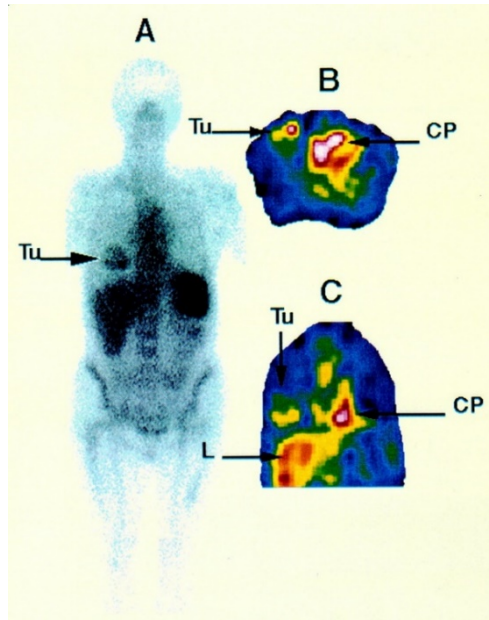
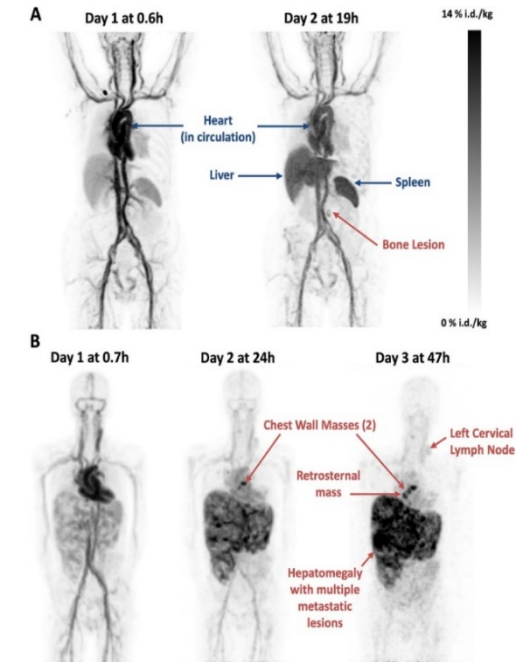


Fig. 1. Scintigraphic planar images from four cases with sarcoma are shown: A: a fibrosarcoma of the iliac region; B: angiosarcoma of the maxillary sinus; C: Ewing sarcoma of the femur; D: Kaposi sarcoma of the palmar area.



<sup>111</sup>In-DTPA-labeled pegylated liposomes in head and neck cancer  
Clin Cancer Res, 2001, 7: 243,

Doxil-99mTc-DTPA in sarcoma  
Acta Oncologica Vol. 39, pp. 207–211, 2000

<sup>64</sup>Cu-labeled HER2-targeted PEGylated liposomal doxorubicin in breast cancer  
Clin Cancer Res, 2017 23: 4190

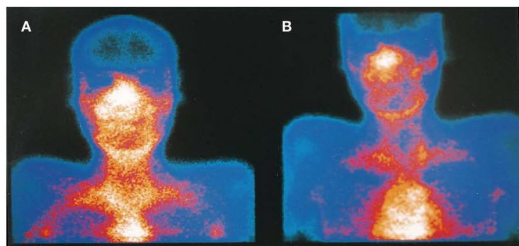
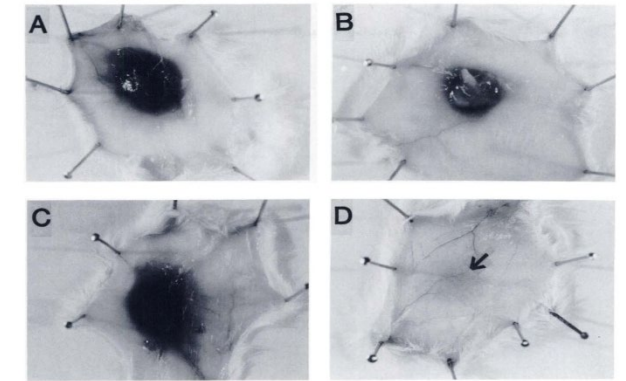
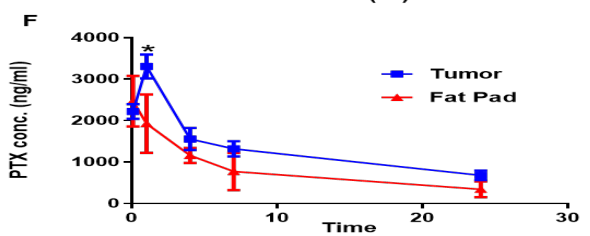
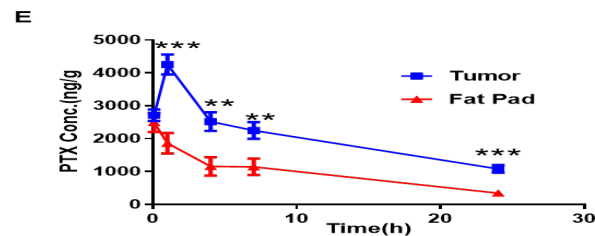
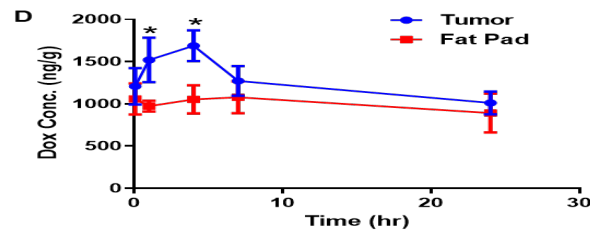
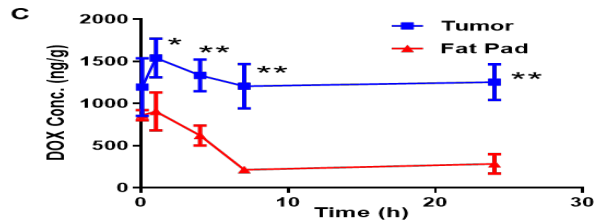
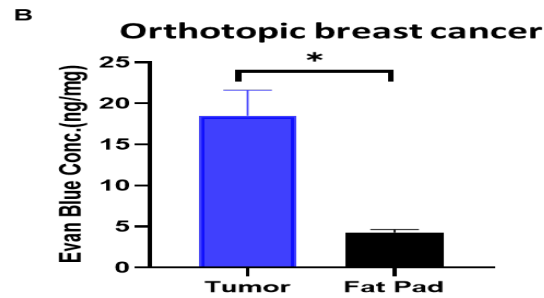
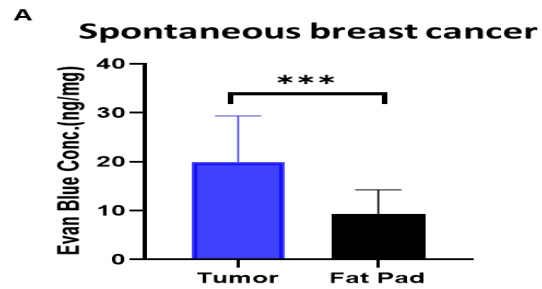
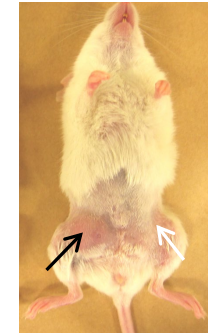
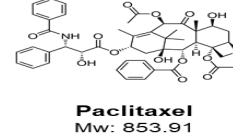
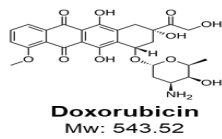
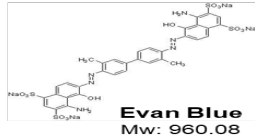


Fig 4. Planar scintigrams of a large nasopharyngeal carcinoma after <sup>99m</sup>Tc-DTPA-Caelyx administration, before (A) and after (B) the delivery of 40 Gy of radiotherapy.

99mTc-DTPA–Doxil in Lung and Head and Neck Cancer  
Journal of Clinical Oncology,  
Vol17, No11 (November), 1999: pp3512-3521

# Tumor EPR was Observed for Small Molecules Breast Tumors vs. Normal Breast Tissues



EPR was first discovered in 1986 in xenograft cancer models using radioactive labeled proteins and small molecule Evans Blue Tumor vs. normal tissues

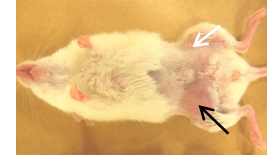
Matsumura and Maeda  
Cancer Res, 1986, 46, 6387

# Enhanced NanoMedicine Accumulation in Tumor by EPR was only Achieved in subcutaneous and orthotopic cancers, but not in transgenic spontaneous breast cancers

## Nanomedicines vs. free drugs (or clinically standard formulation) in tumors



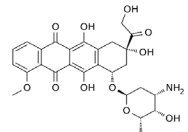
Subcutaneous Cancer



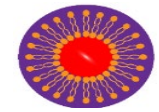
Orthotopic Cancer



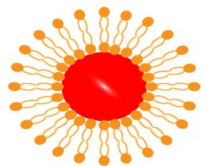
Spontaneous Cancer



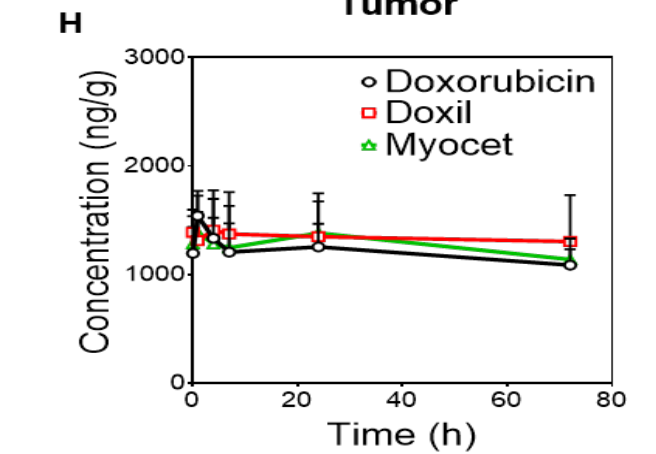
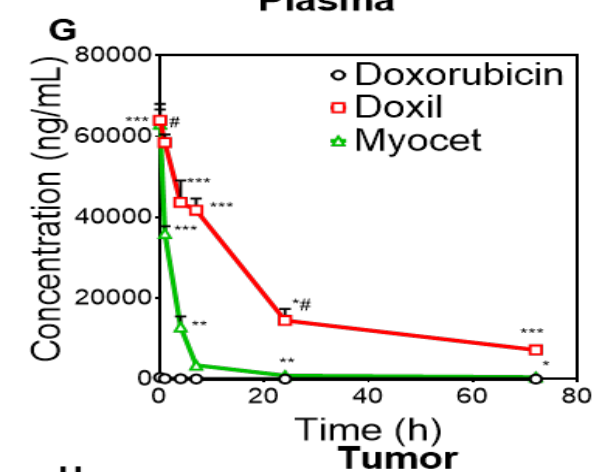
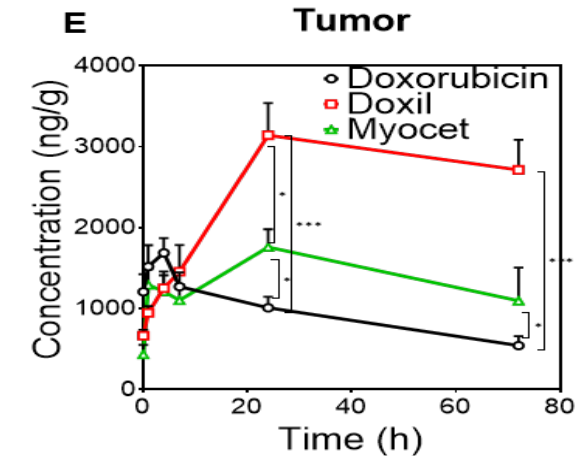
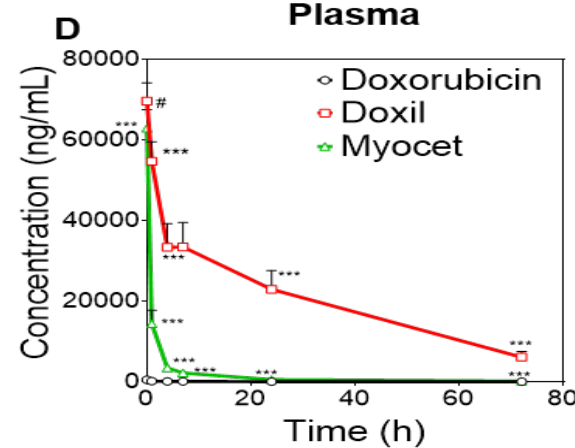
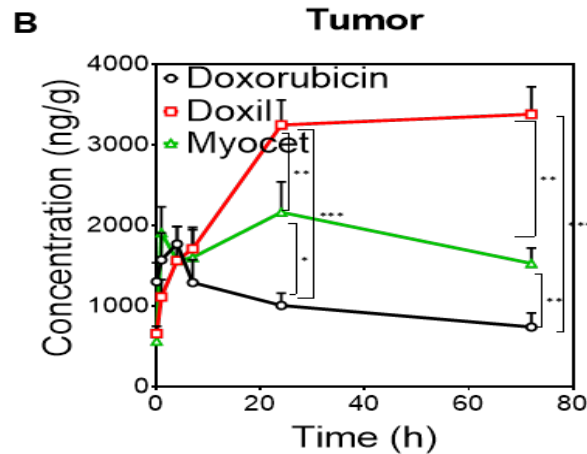
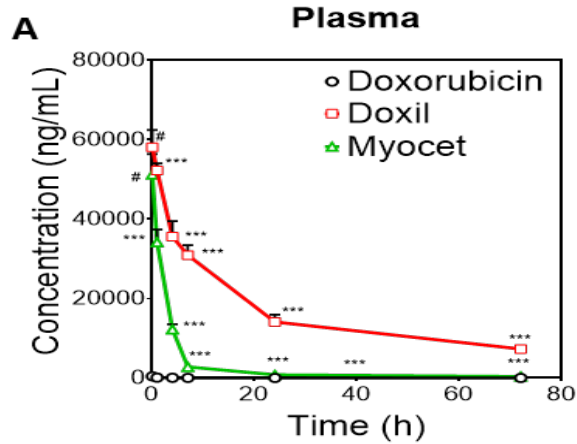
Doxorubicin Solution



Doxil  
≈85 nm



Myocet  
≈180 nm

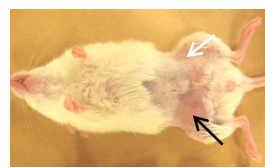




The enhanced accumulation of Nanomedicine by tumor EPR was achieved in subcutaneous and orthotopic cancers, but not in transgenic spontaneous breast cancers  
 Nanomedicines vs. free drugs (or clinically standard formulation) in tumors



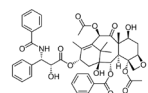
Subcutaneous Cancer



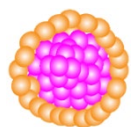
Orthotopic Cancer



Spontaneous Cancer



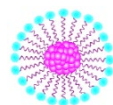
Taxol (micelle)  
13 nm



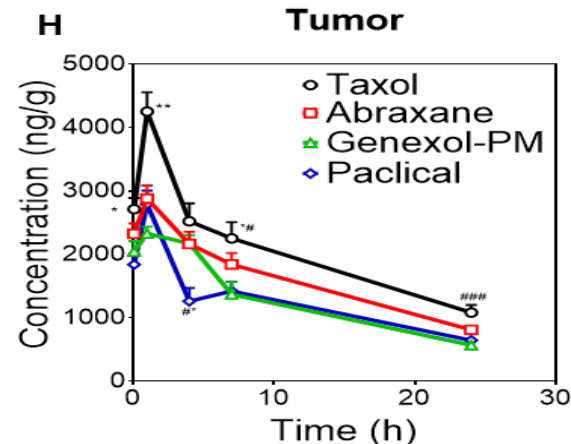
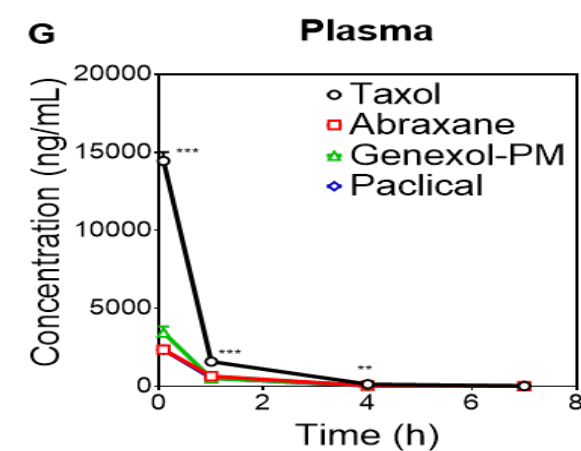
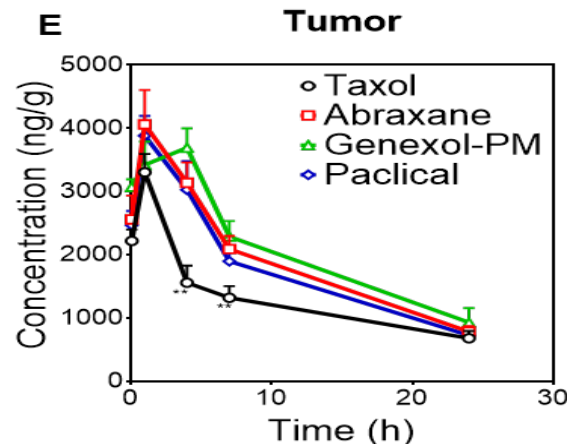
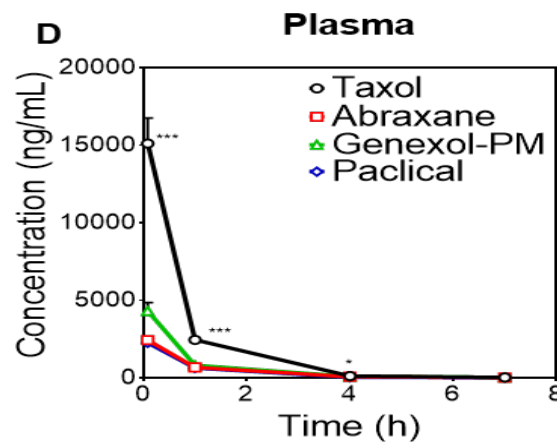
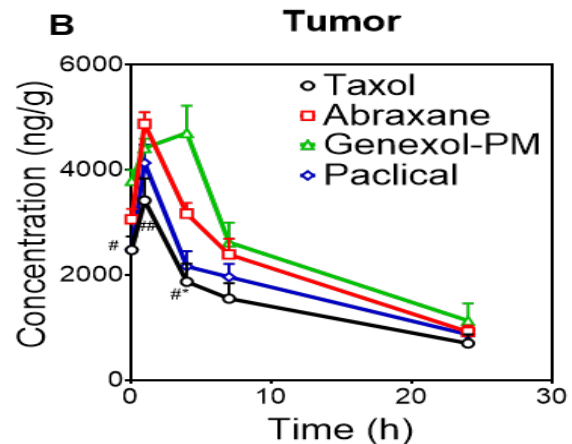
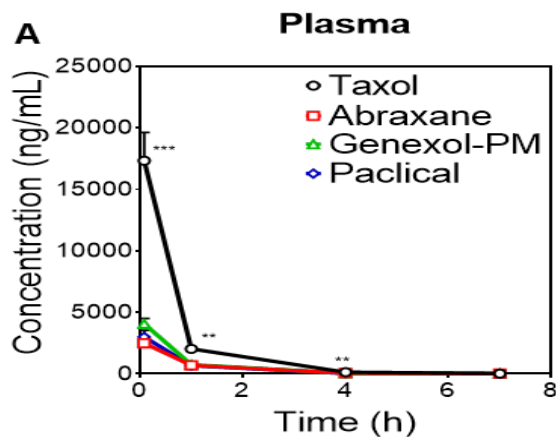
Abraxane  
≈136 nm



Genexol-PM  
≈22 nm

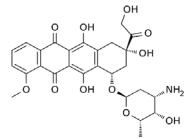


Paclical  
≈42 nm

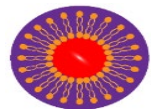


# **Long Systemic Circulation Should Not Be a Universal Nanomedicine Design Criterion**

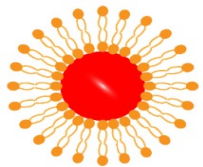
# Long Circulating NanoMedicines May Reduce Tumor Penetration



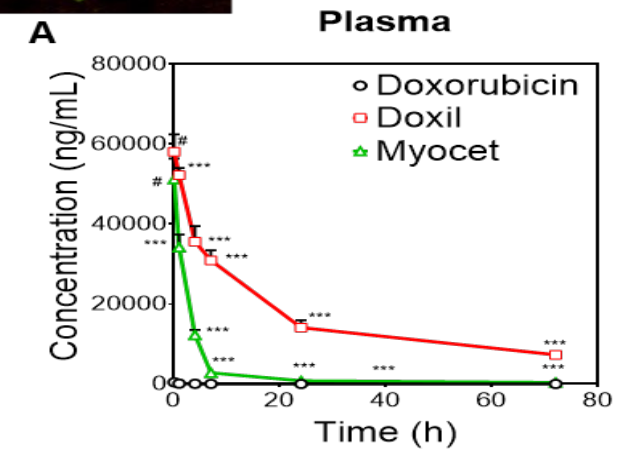
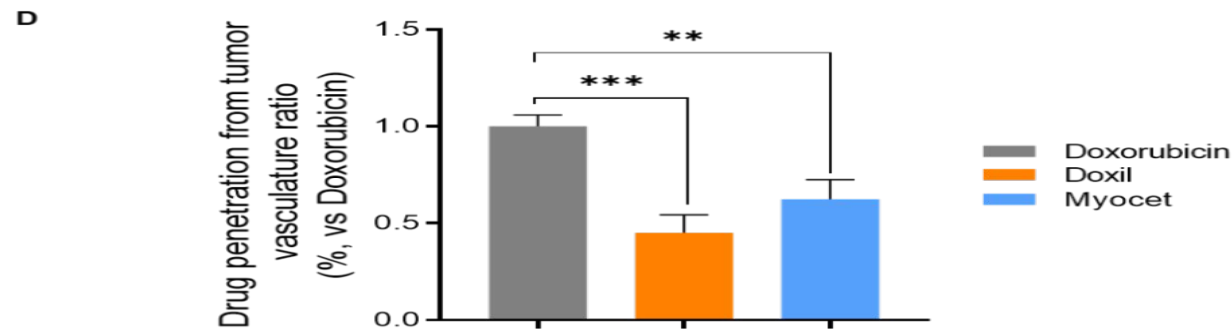
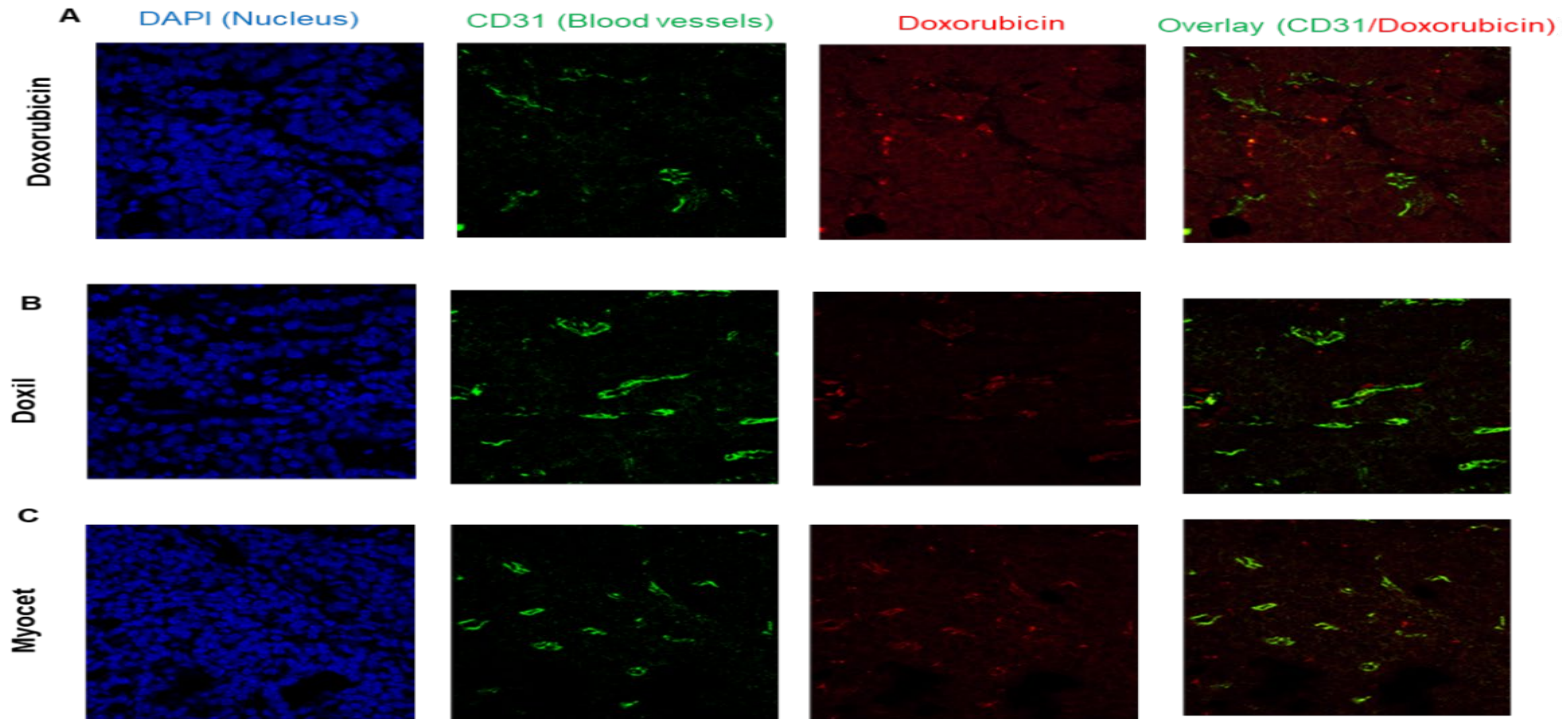
Doxorubicin Solution



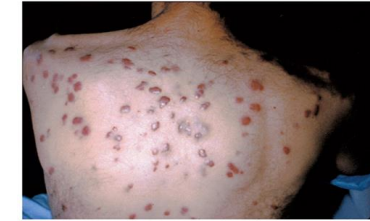
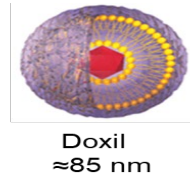
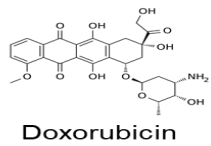
Doxil  
≈85 nm



Myocet  
≈180 nm



# Long-circulating Nanomedicines Do not Universally Decrease Normal Tissue Distribution, but Change the Tissue Distribution to Alter Efficacy/Safety

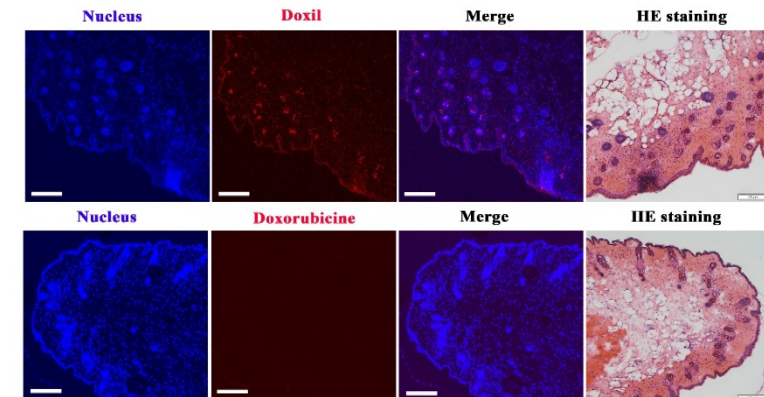
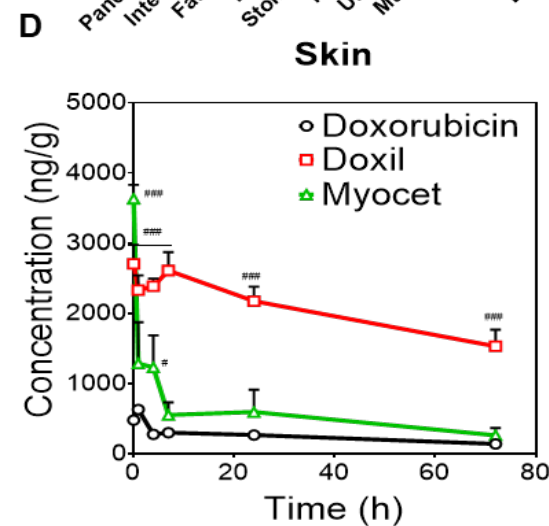
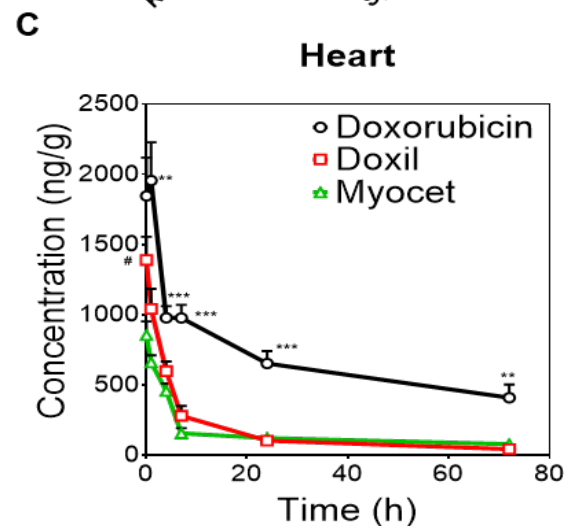
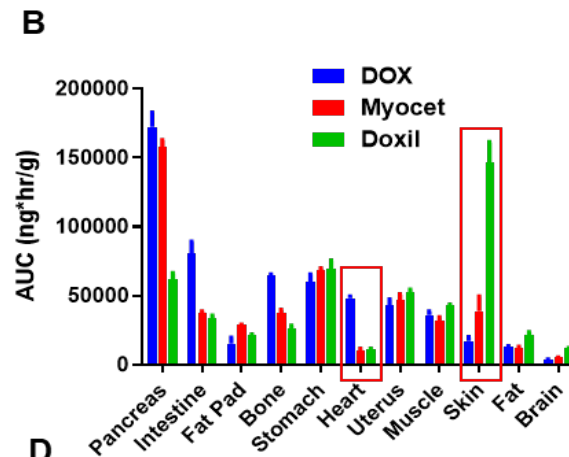
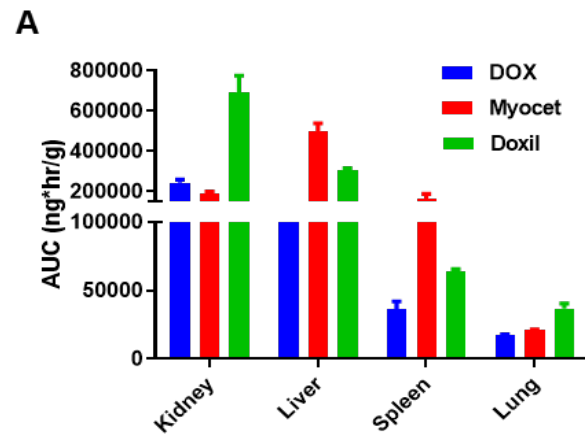


AIDS-related Kaposi's sarcoma

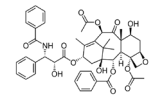


Hand-foot-syndrome

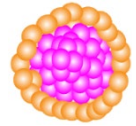
<https://www.eviq.org.au/clinical-resources/side-effect-and-toxicity-management/hair-skin-and-nails/1416-hand-foot-syndrome-associated-with-chemotherapy>



# Short-circulating NanoMedicines Have Distinct Delivery Efficiency to Different Cell Types in Tumor Microenvironment, Which is Associated With Clinical Efficacy.



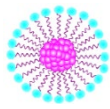
Taxol (micelle)  
13 nm



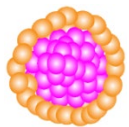
Abraxane  
≈136 nm



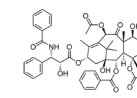
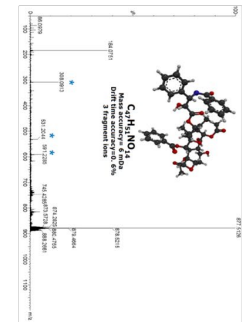
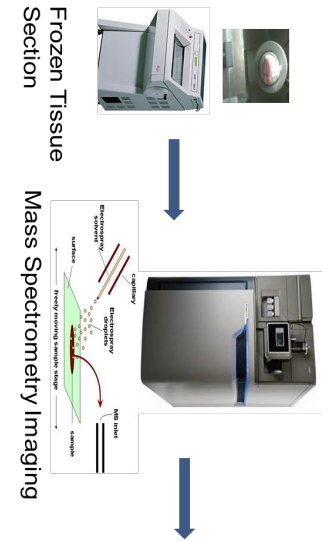
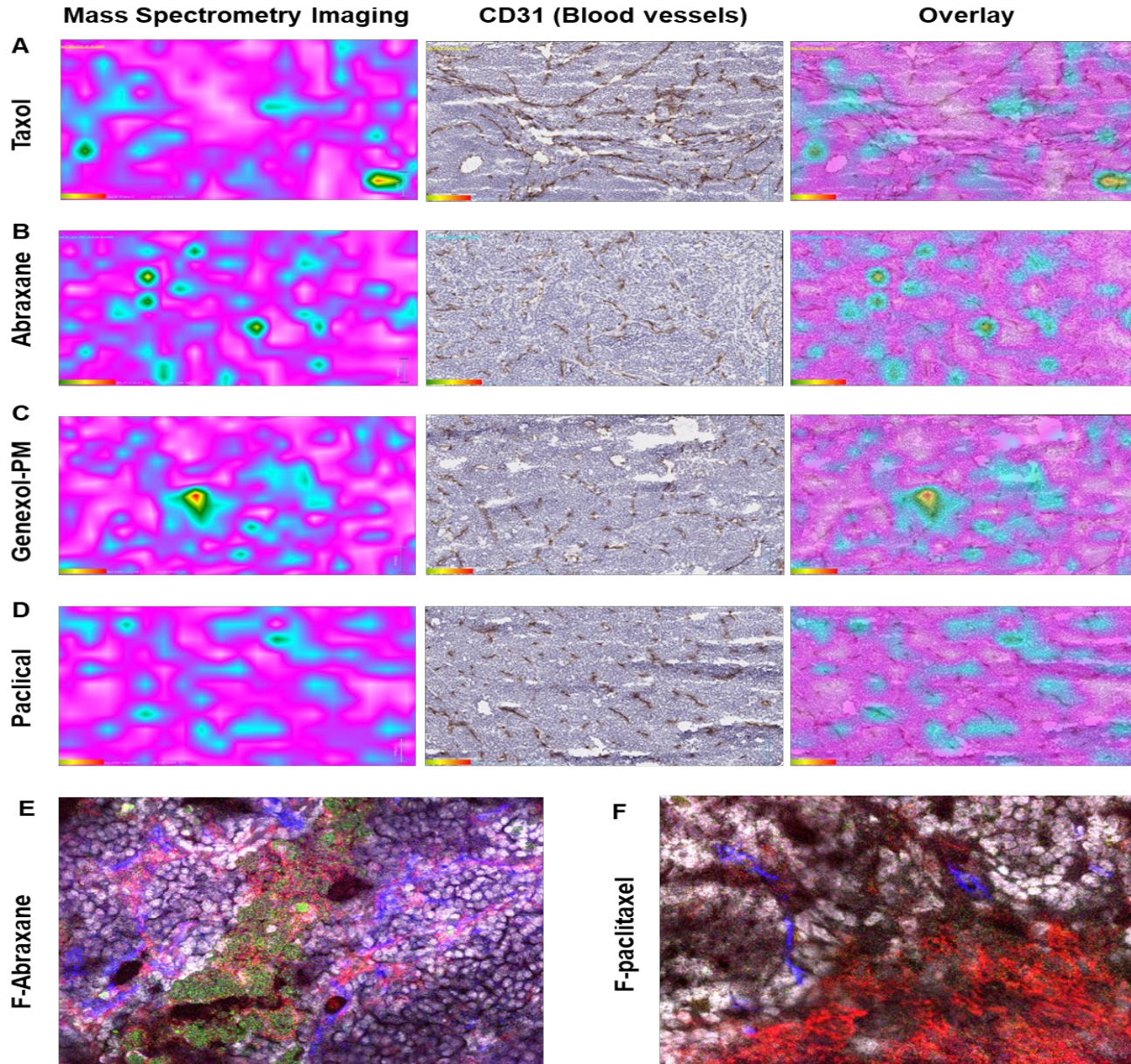
Genexol-PM  
≈22 nm



Paclical  
≈42 nm

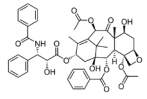


Abraxane  
≈136 nm

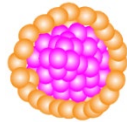


Taxol (micelle)  
13 nm

# Short-circulating NanoMedicines Decrease Blood Concentration and Alter Tissue Exposure, Which May Reduce Adverse Events in Blood Compartment but Increase Toxicity in Other Organs.

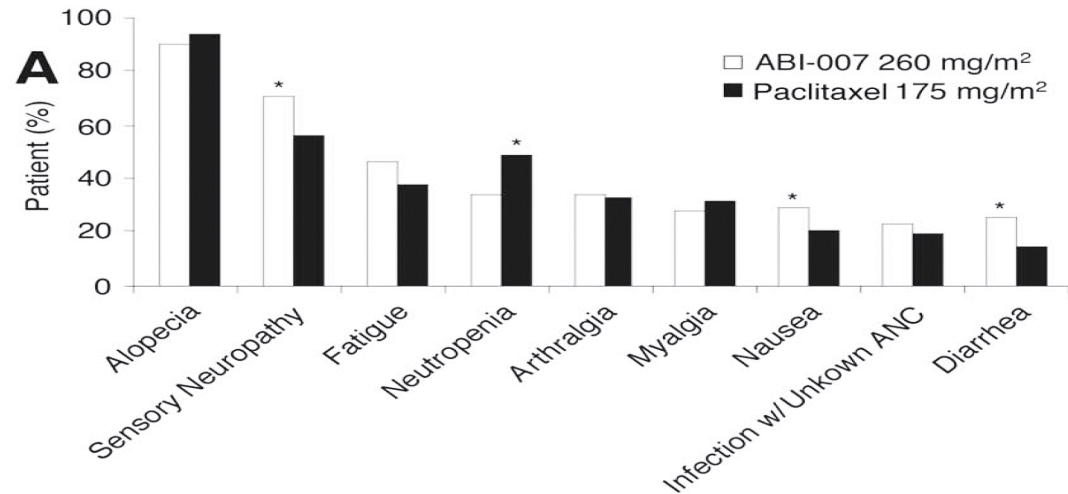
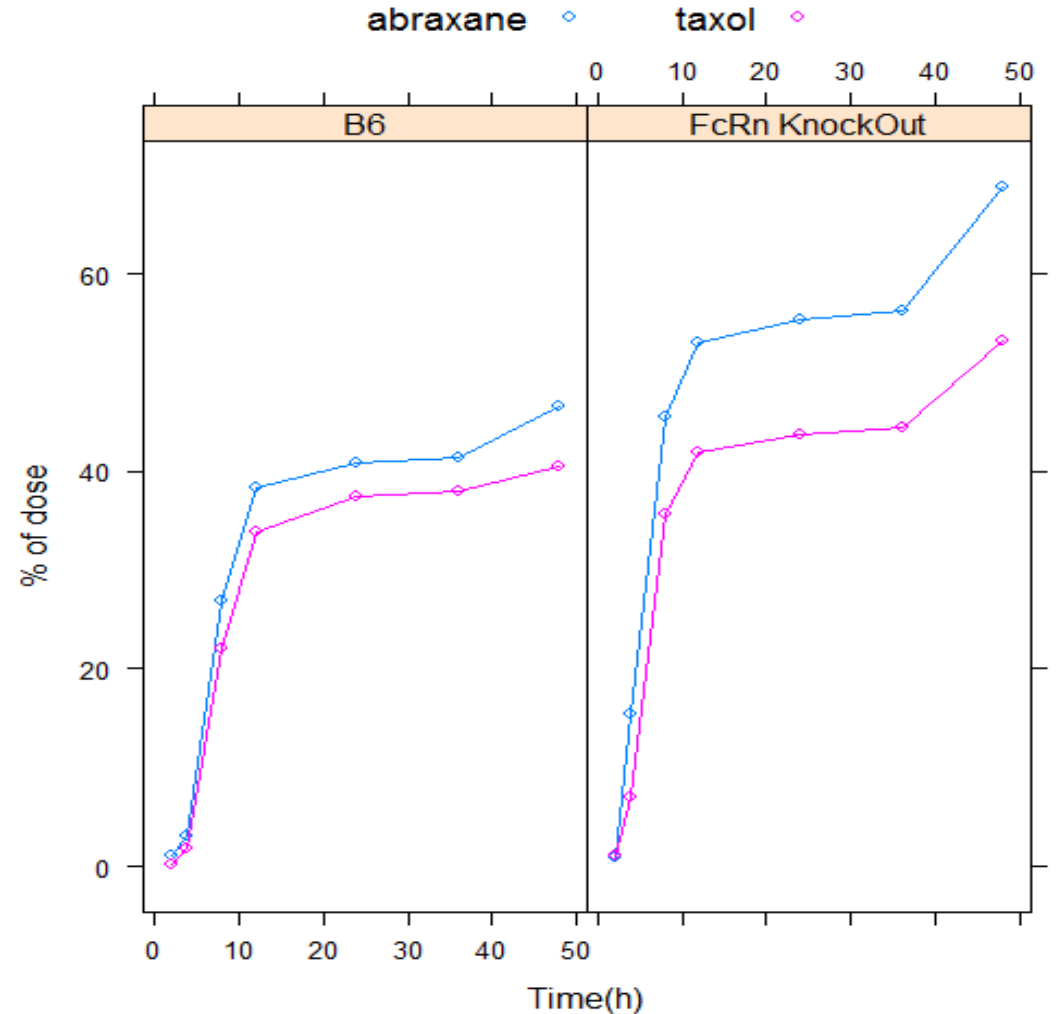
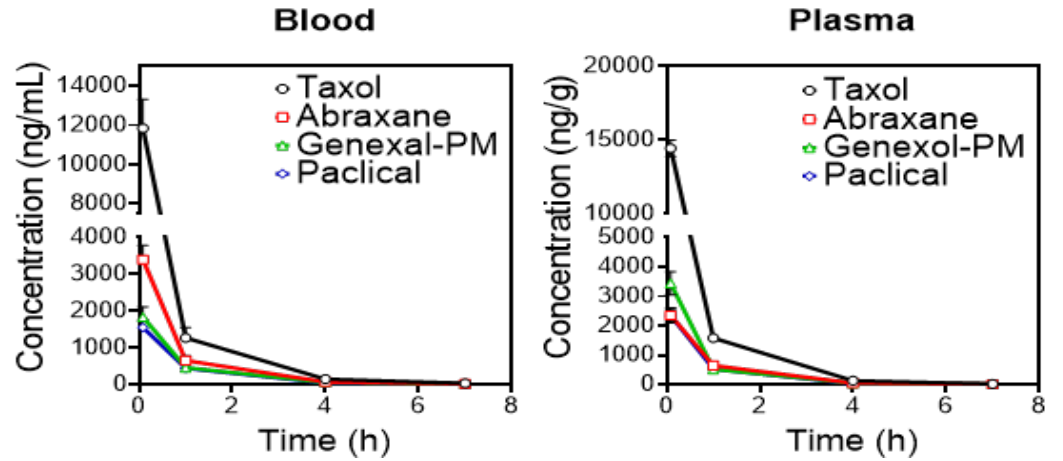


Taxol (micelle)  
13 nm



Abraxane  
≈136 nm

## Paclitaxel Excreted in Feces

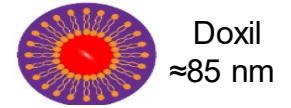


# **A Universal Nanodelivery Platform for Different Drugs May Not Be Feasible**

# A Universal Nanodelivery Platform for Different Drugs May Not Be Feasible

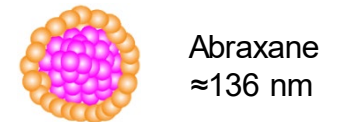
- PEGylated liposome

- Encapsulate doxorubicin to increase efficacy in ARKS, reduce cardiotoxicity
- Encapsulate paclitaxel?
  - Reduce efficacy? alter efficacy?
  - Reduce toxicity? Which one? Neutropenia? Neuropathy?
  -



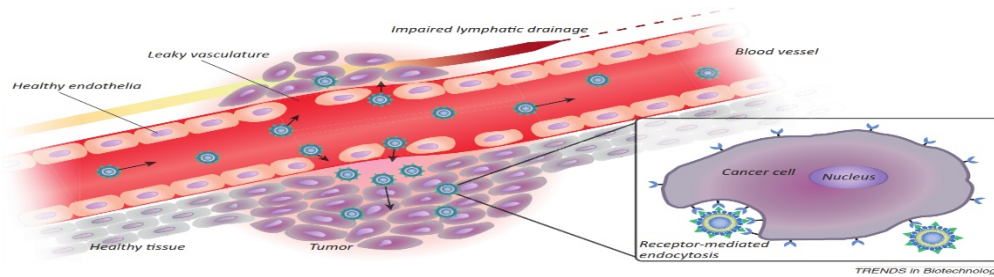
- Albumin nanoparticle

- Encapsulate paclitaxel to increase efficacy in breast cancer, lung cancer, pancreatic cancer; reduce neutropenia, increase neuropathy
- Encapsulate doxorubicin?
  - Increase efficacy? reduce efficacy?
  - Increase cardiotoxicity?





# What Went Wrong with Anticancer NanoMedicine Design and How to Make It Right



Sun, D et al. ACS Nano, 2020, 14: 12281-12290  
Luan, and Sun et al. Biomaterial, 2021, 275: 120910

## Universal NanoDelivery Platform

- ❖ Tumor accumulation by Enhanced Permeability Retention (EPR) to improve efficacy
- ❖ Long circulation and high plasma concentration to reduce normal organ accumulation and toxicity
- ❖ One universal nanodelivery platform for different drugs

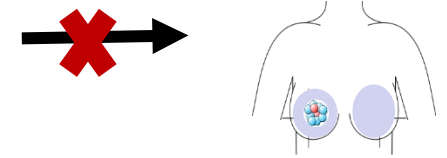


**Preclinical Evaluation**  
Exaggerated Delivery Efficiency  
and Anticancer Efficacy



Subcutaneous Cancer

**Clinical Translation**  
Altered Efficacy and  
Adverse Events



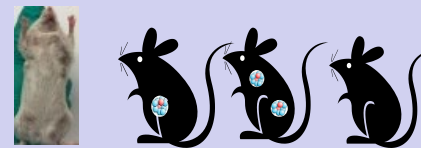
Cancer Patients

## Drug-Specific NanoDelivery Systems

- ❖ Drug-specific  
Overcome intrinsic shortcomings of drug's physicochemistry, Pharmacokinetics, Pharmacodynamics, and efficacy/safety
- ❖ Nano Carrier Specific  
Alter tissue distribution for new efficacy/safety
- ❖ Cancer type-Specific  
Different cancer types may need different nano-carriers
- ❖ Cell Type Specific  
Deliver to different type of cells in tumor microenvironment

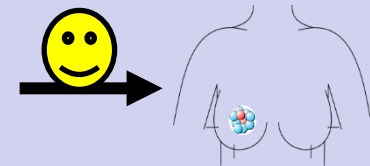


**Preclinical Evaluation**  
Altered Tissue Distribution  
and Efficacy/Toxicity



Spontaneous or Metastatic Cancer

**Clinical Translation**  
Altered Efficacy and Adverse  
Events



Cancer Patients

# III. Biopharmaceutics of NanoVaccines

- Physico-chemical properties, nanoformulations, size, stability, surface etc.
- Alters lymph node delivery, localization, interaction with macrophages, DCs,
- Changes B cell and T cell immunity
- Impacts clinical dose/efficacy/safety

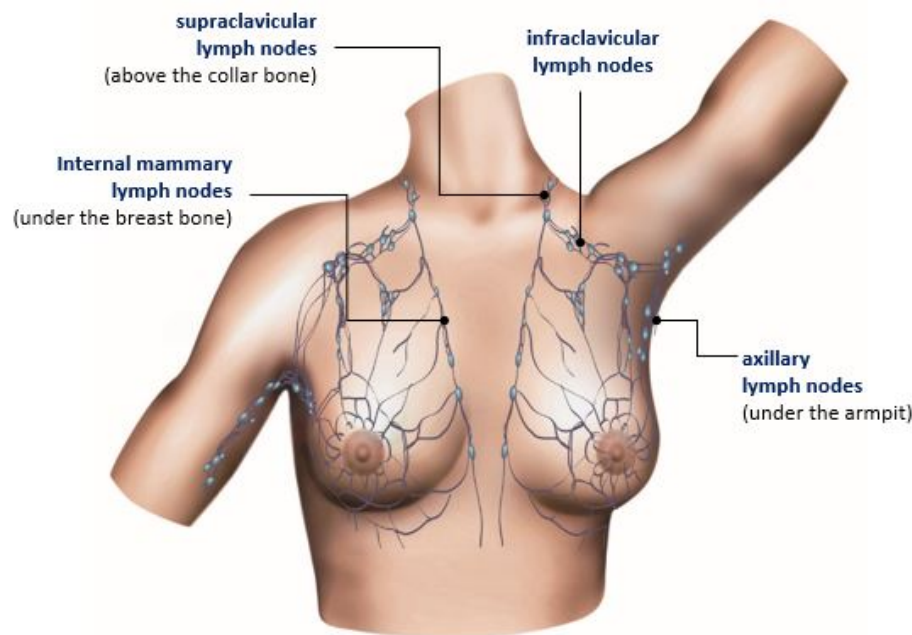
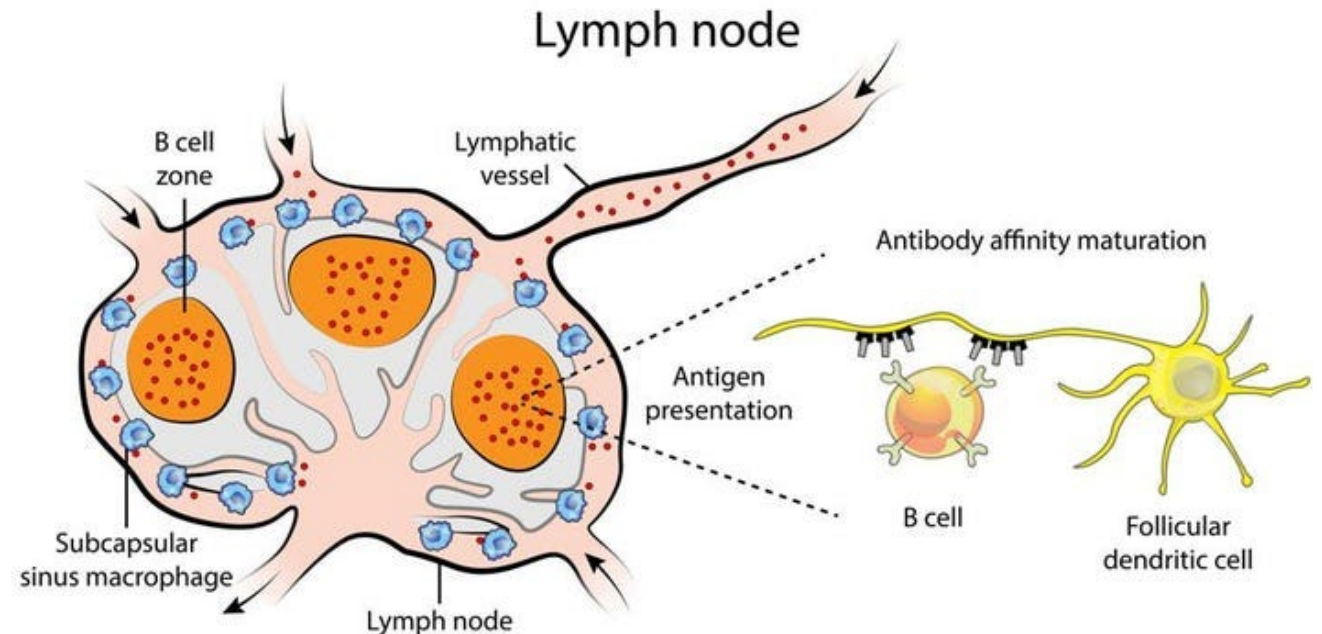


Illustration of lymph nodes near the breast

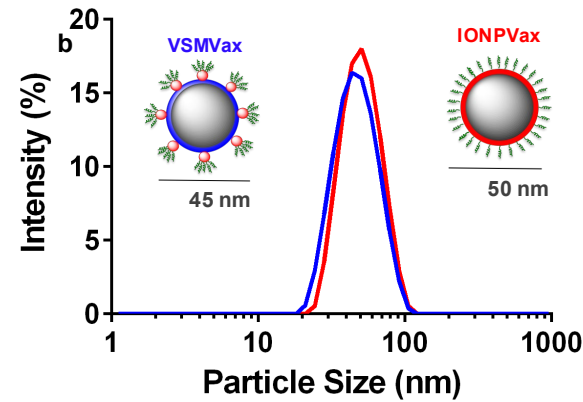
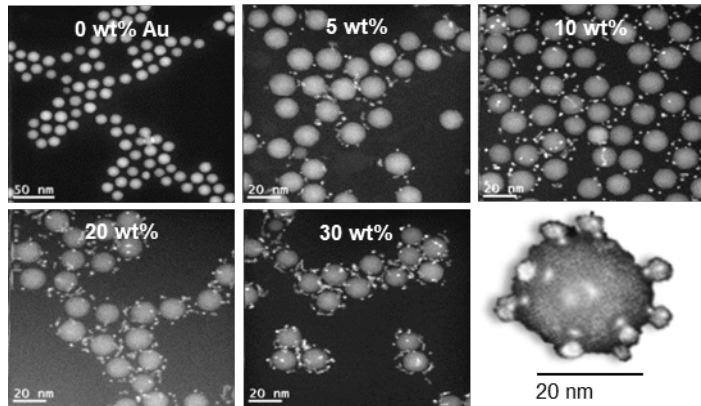
<https://myjourney.org.au/article/2160>



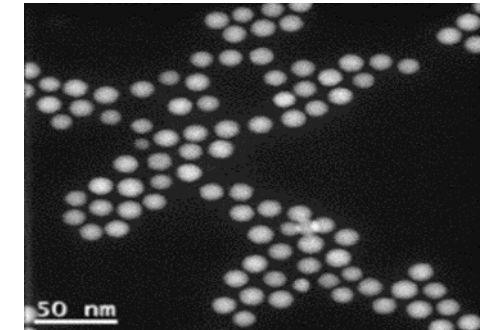
<https://www.forbes.com/sites/brucelee/2021/03/03/can-this-covid-19-coronavirus-vaccine-side-effect-be-mistaken-for-cancer/?sh=72511d2a76e9>

# Modification of NanoVaccine Surface (with same particle size, same zeta potential, same antigen density) Alters Delivery to Lymph Nodes (SC Injection)

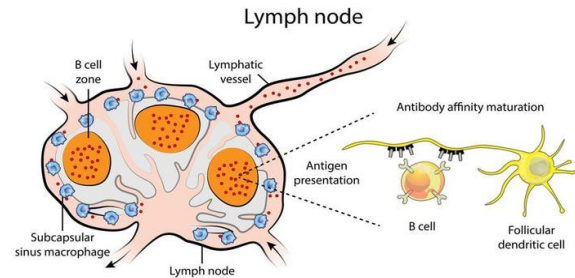
## Virus Spilke Mimicry (VSM) NanoVaccine



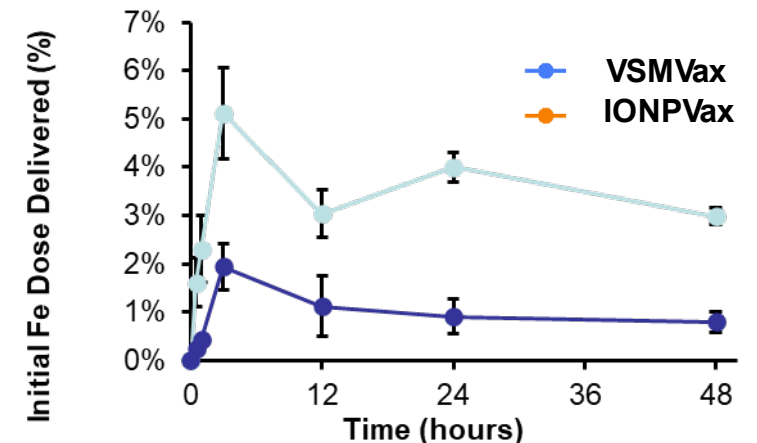
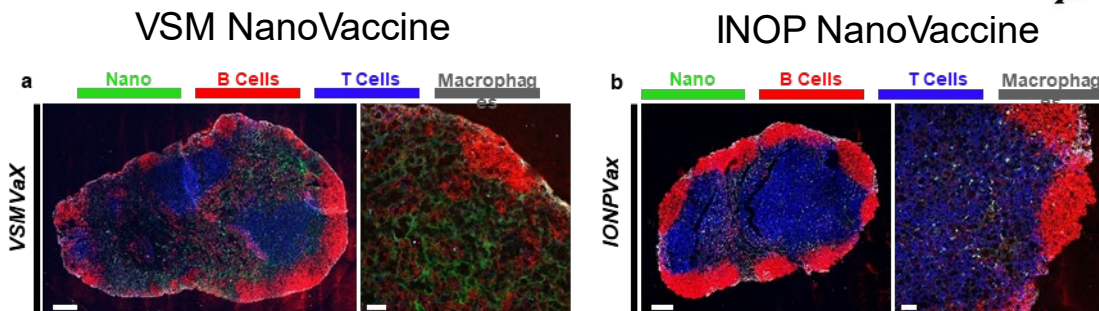
## INOP NanoVaccine



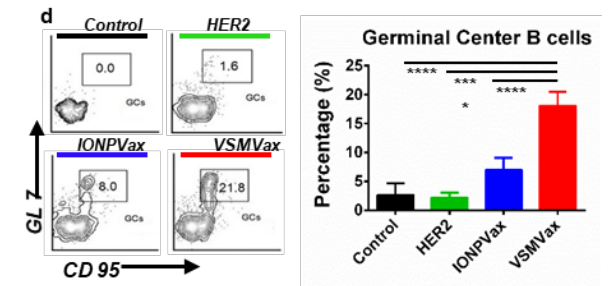
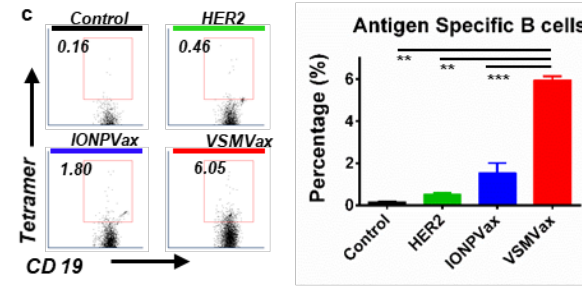
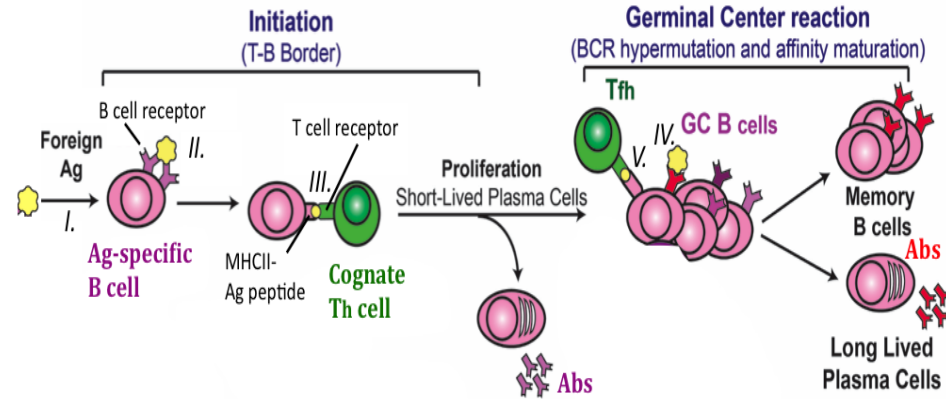
VSM NanoVaccine delivers to distinct region of Lymph nodes than INOP vaccine



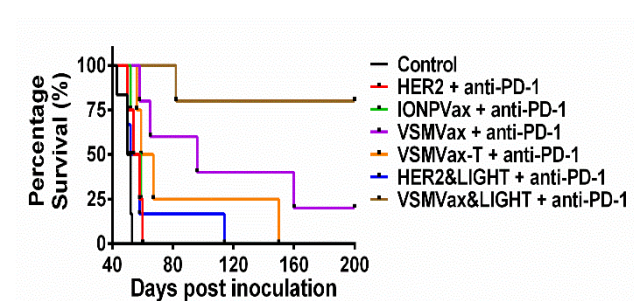
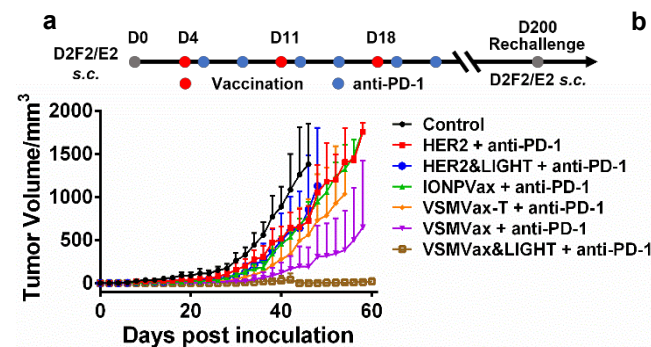
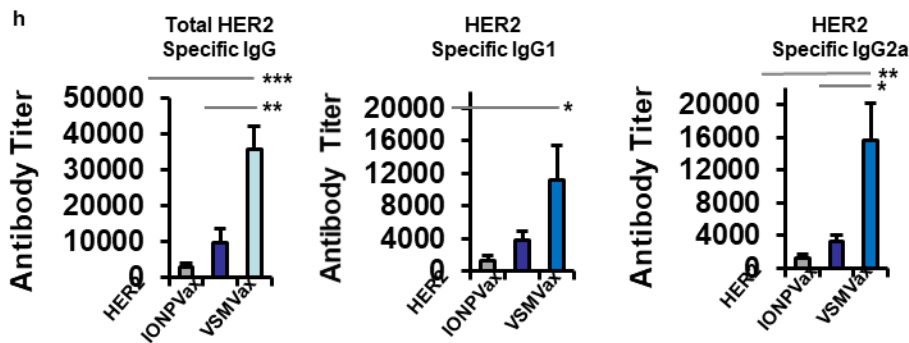
VSM NanoVaccine delivers to more to Lymph nodes than INOP vaccine



# Modification of NanoVaccine Surface (with same particle size, same zeta potential, same antigen density) Alters Geminal Center B cells and Antigen-Specific B cells (SC Injection)



# Modification of NanoVaccine Surface (with same particle size, same zeta potential, same antigen density) Alters Antibody Productions and Efficacy (SC Injection)



# Implication of Biopharmaceutics of NanoMedicines / NanoVaccines

- Biopharmaceutics for Nanomedicines / NanoVaccines
  - Interplay among physico-chemical properties and nanoformulations, exposure/localization in disease targeted tissues and lymph nodes, and balance of clinical dose/efficacy/toxicity
- Implication
  - Ensure Product Quality
    - What are the product quality attributes to be controlled?
    - What are the specifications of the products? Why?
  - Regulatory approval
    - 505(b)(2) pathway based on plasma exposure profile or tissue exposure profiles? What tissue exposure profile? How to monitor?
    - What data need to be submitted for products approval?
  - Design and Development Criteria
    - NanoMedicine design criteria?
    - NanoVaccine design criteria?



# Sun Lab Team

