The *nab*® Platform : From Bench to the Clinic and Beyond

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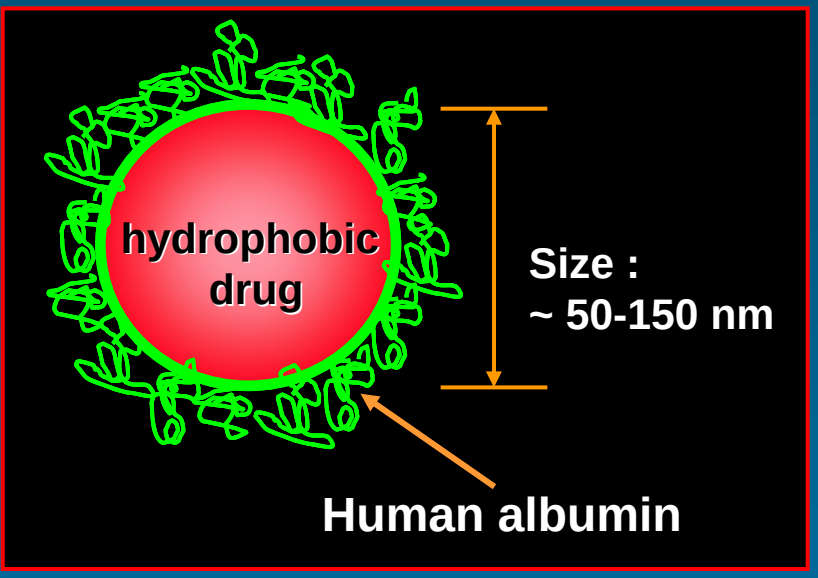
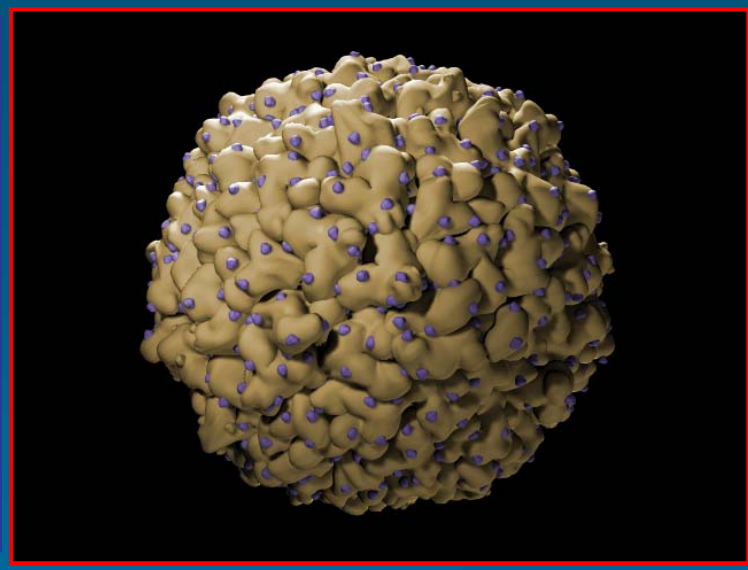
Nanoparticle Albumin-bound (*nab*) Platform

- Technology based on albumin + insoluble drug
- The *nab* platform exploits unique transport properties of albumin (gp60 and SPARC) that can result in high intratumoral concentrations
- ABRAXANE (paclitaxel + albumin) is recognized as the first true “bottom up” nanotechnology pharmaceutical product to be approved and marketed
- Approved in 38 countries for treatment of metastatic breast cancer (MBC)





Decreased Toxicity (LD_{50}) of *nab*-paclitaxel vs cremophor-paclitaxel

Abraxane

Reconstituted
Paclitaxel 5 mg/ml
Albumin ~45 mg/ml
No Surfactants/Solvents

nab-paclitaxel vs Cremophor-paclitaxel

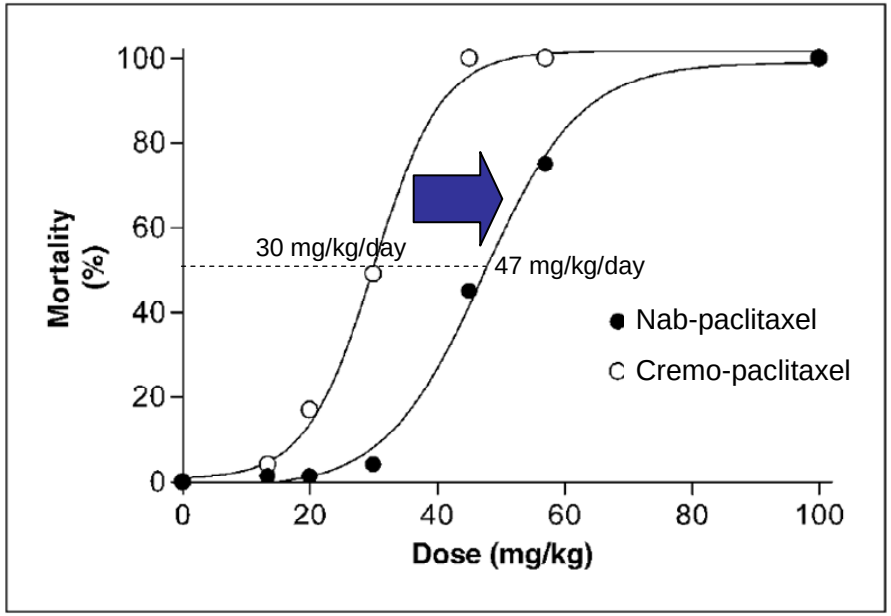
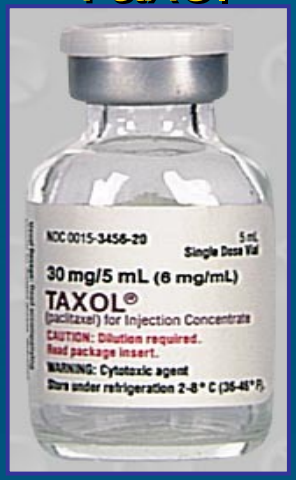


Fig. 1. LD_{50} for Cremophor-based paclitaxel and ABI-007. Mortality data from all tumor models as well as from non-tumor-bearing animals were plotted versus dose and curve-fitted using the Boltzmann sigmoidal equation. ABI-007 was significantly less toxic than Cremophor-based paclitaxel. $P = 0.017$ (ANOVA).

	LD_{50} Mice	Human MTD
Cremo-paclitaxel	: 30.0 mg/kg	175 mg/m^2
Nab-paclitaxel	: 47.0 mg/kg	300 mg/m^2

Taxol



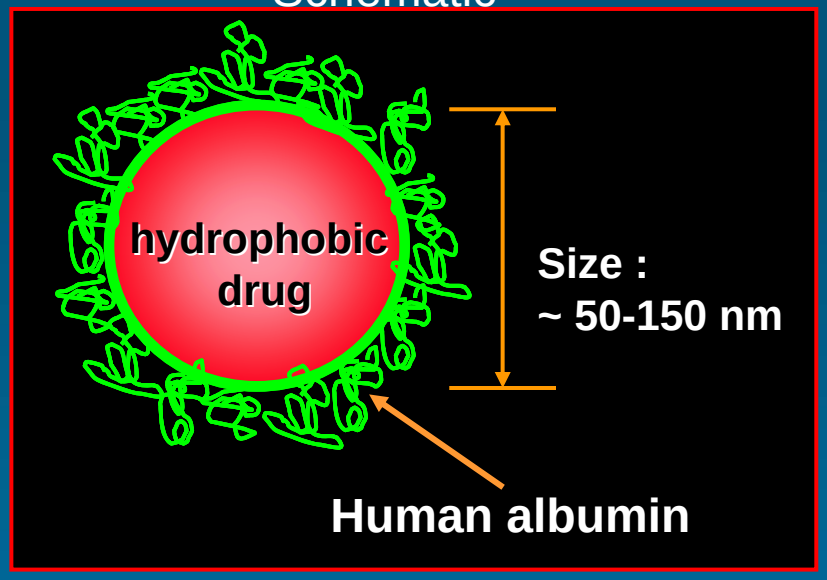
Supplied As
Paclitaxel 6 mg/ml
Cremophor 537 mg/ml
Ethanol 396 mg/ml

Desai N, et al. *Clin Cancer Res* 2006;12(4), 1317-24

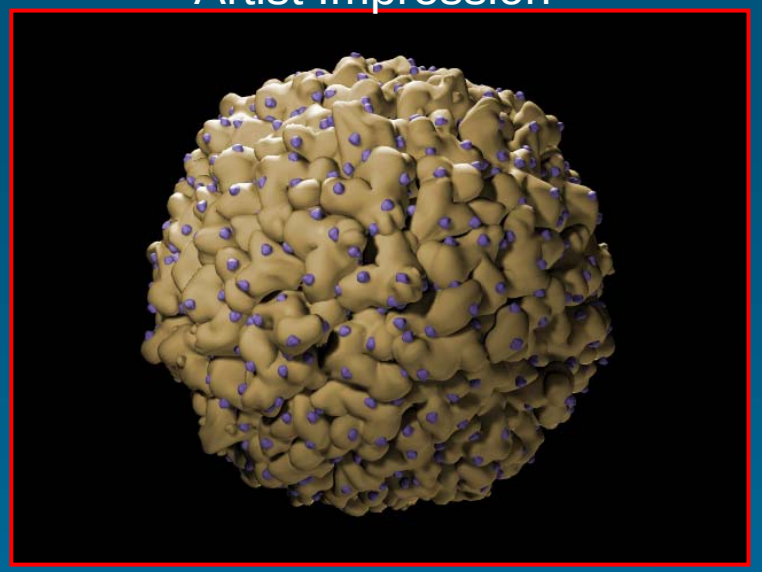
Characterization of Abraxane (*nab*-paclitaxel)

- Multiple orthogonal techniques are required since these systems have complex morphology and composition
  - Particle size (light scattering)
  - Surface Charge (Zeta potential)
  - Amorphous nature of paclitaxel in the nanoparticle (X-Ray Diffraction)
  - Morphology (TEM and Cryo-TEM)
  - Other specific tests defined by nature of the nano construct

Schematic



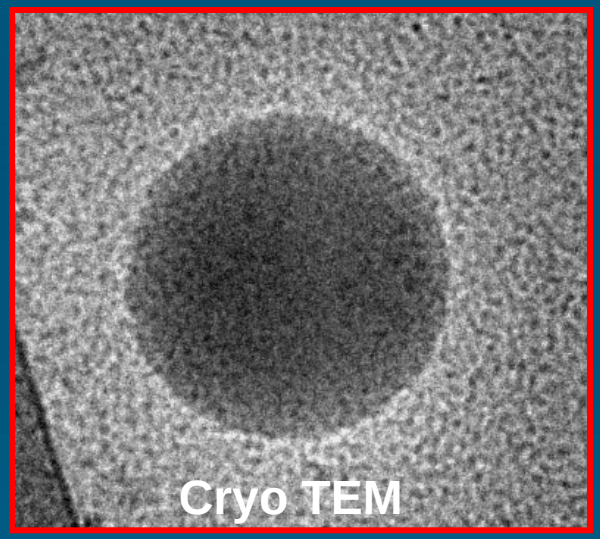
Artist Impression

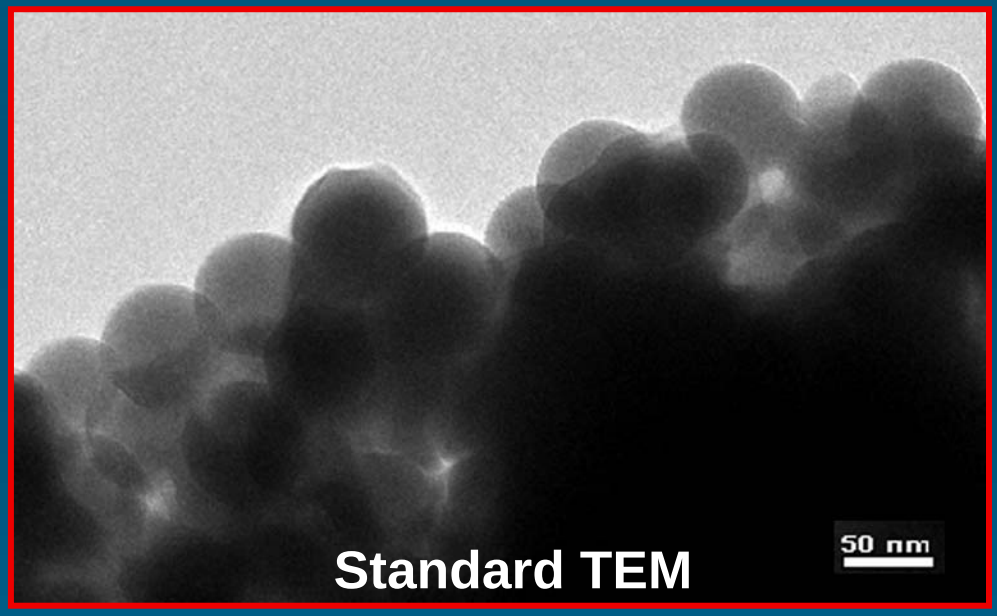


Note: Inadequate sample preparation techniques for nano constructs can easily result in artifacts

Electron Microscopy

- EM data supports proposed structure of nanoparticles
  - Size, amorphous nature
  - Amorphous nature also supported by XRPD



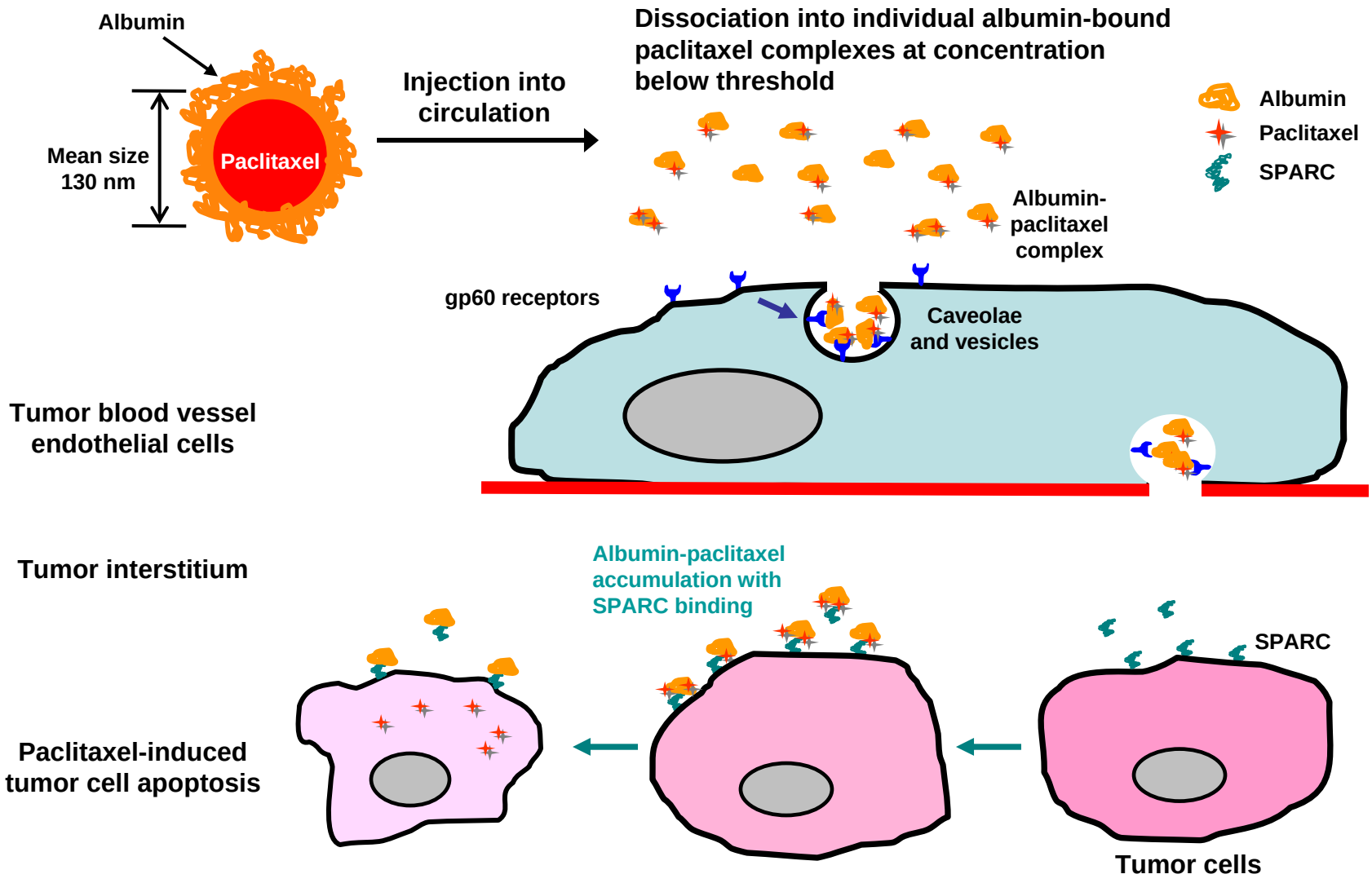


Preclinical Requirements for Nanotech products (e.g., *nab*-paclitaxel)

- Standard battery of toxicology studies are sufficient to establish safety
- Design/Conduct studies to understand the disposition of the ‘nano-construct’ invivo
- Establish unique mechanism of action/transport (MOA) if relevant
- Design target-specific studies to establish efficacy

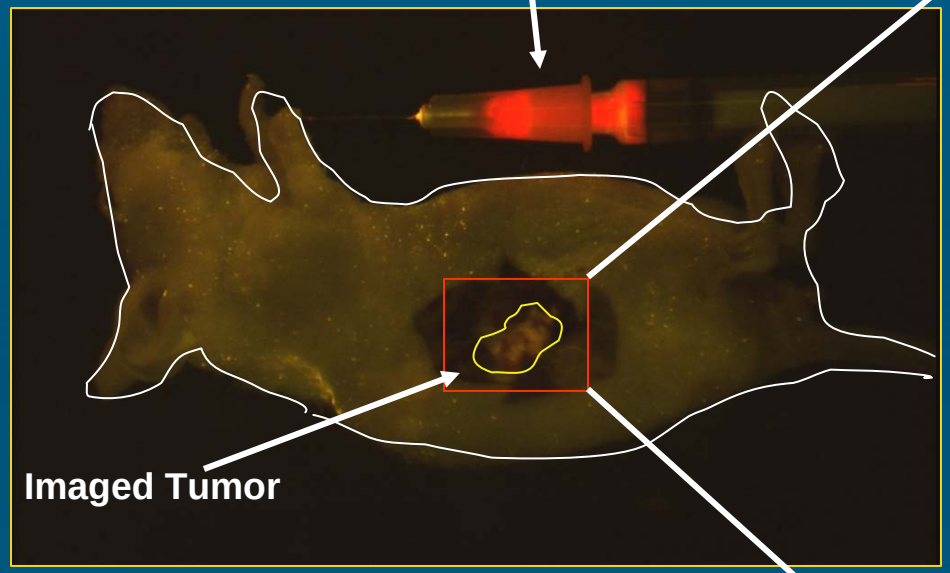
nab Technology Platform: Harnessing Endogenous Albumin Pathways Through Two Postulated Mechanisms of Action

1. Active receptor-mediated transport (transcytosis) by gp60 and caveolae
2. Active binding of albumin-drug complex by SPARC in tumor



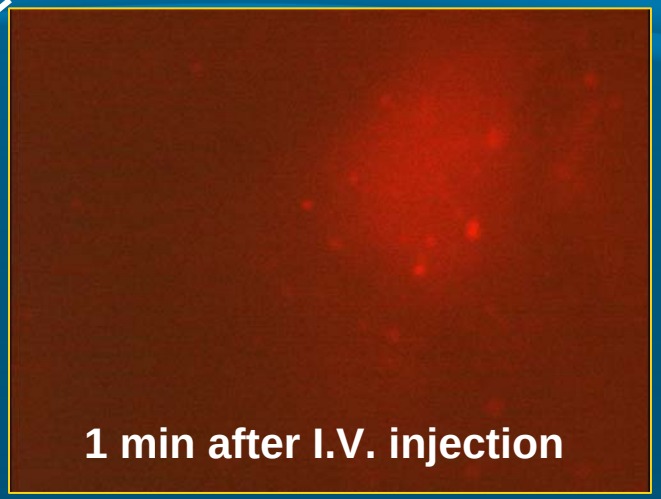
Rapid and increased Tumor Accumulation of *nab*-paclitaxel in tumor

Fluorescent *nab*-paclitaxel Nanoparticles* in Syringe injected via tail vein



MOUSE TUMOR MODEL

Imaging under Hg-lamp with 500-550 nm bandpass excitation; **nab*-paclitaxel containing 0.3% Fluorescent Marker



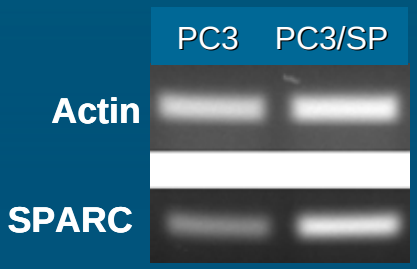
- 33% higher tumor accumulation of paclitaxel over 24 hr confirmed at equi-dose with radiolabelled *nab*-paclitaxel as compared to Taxol ($p<0.0001$)

ABI, data on file and Desai N, et al. *Clin Cancer Res* 2006;12(4), 1317-24

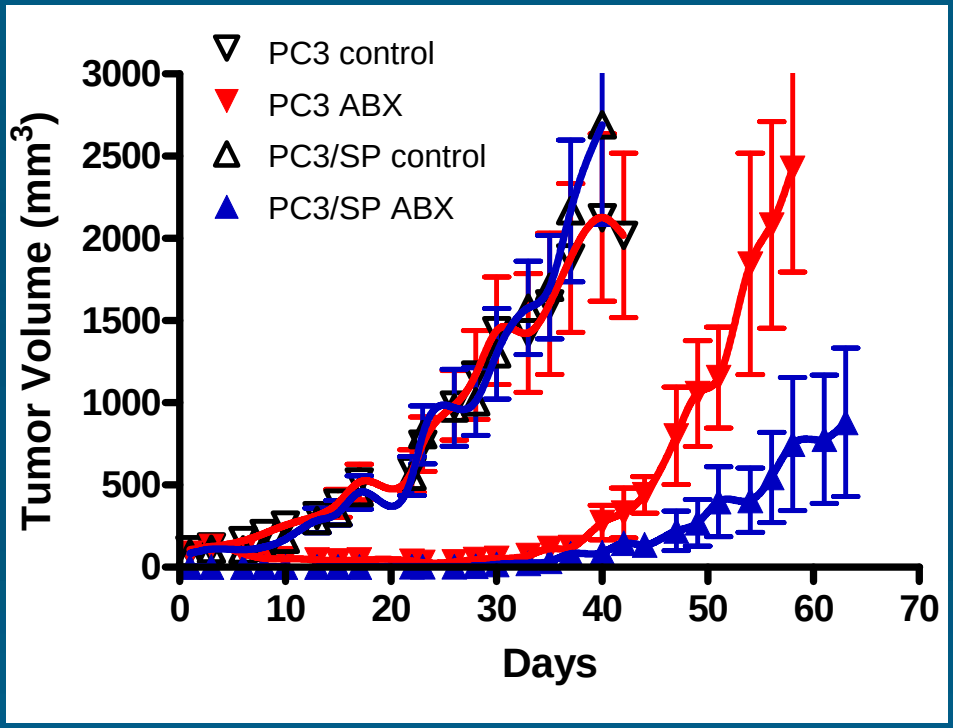
SPARC Expression level in Tumors can predict response to Abraxane

PC3 Human Prostate cancer cell line transfected with expression vector driving expression of SPARC

A. RT-PCR



B. Western blot



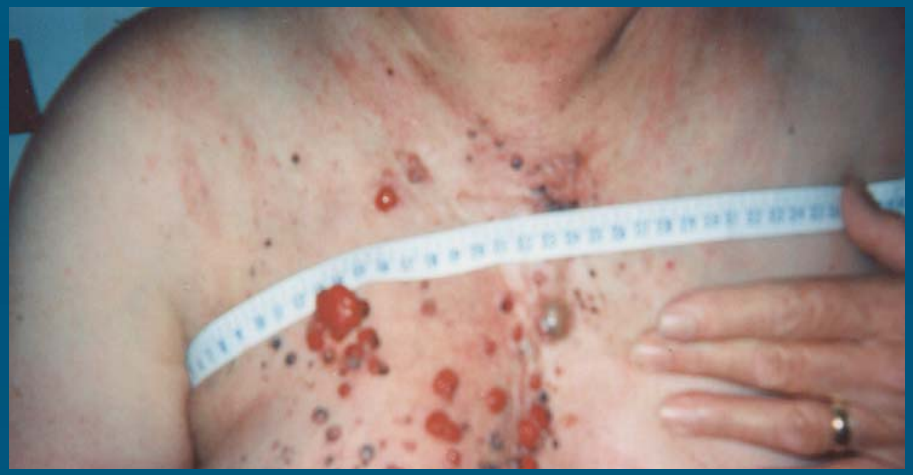
- High SPARC level in transfected PC3/SP results in significantly improved response to Abraxane compared to PC3 wild type ($p < 0.01$)

Desai et al, 2007, Sidney Kimmel Targeting and Drug Delivery Conference, Coronado, CA

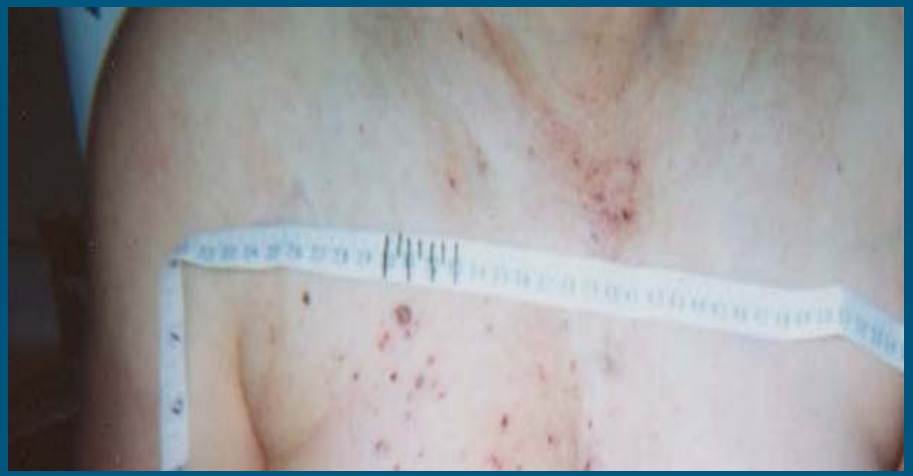
Clinical Efficacy of *nab*-paclitaxel

- Proven efficacy in phase III setting in Metastatic Breast Cancer (MBC) – Jan 2005 FDA approval
- Proven efficacy in phase III setting in non-small cell lung cancer (NSCLC) – data released at ASCO June 2010
- Strong evidence of activity in phase II pancreatic cancer and melanoma

Phase I: Clinical Response in Patients Who Have Failed Taxol Therapy



Patient did not respond to Taxol



Patient responded to Abraxane treatment

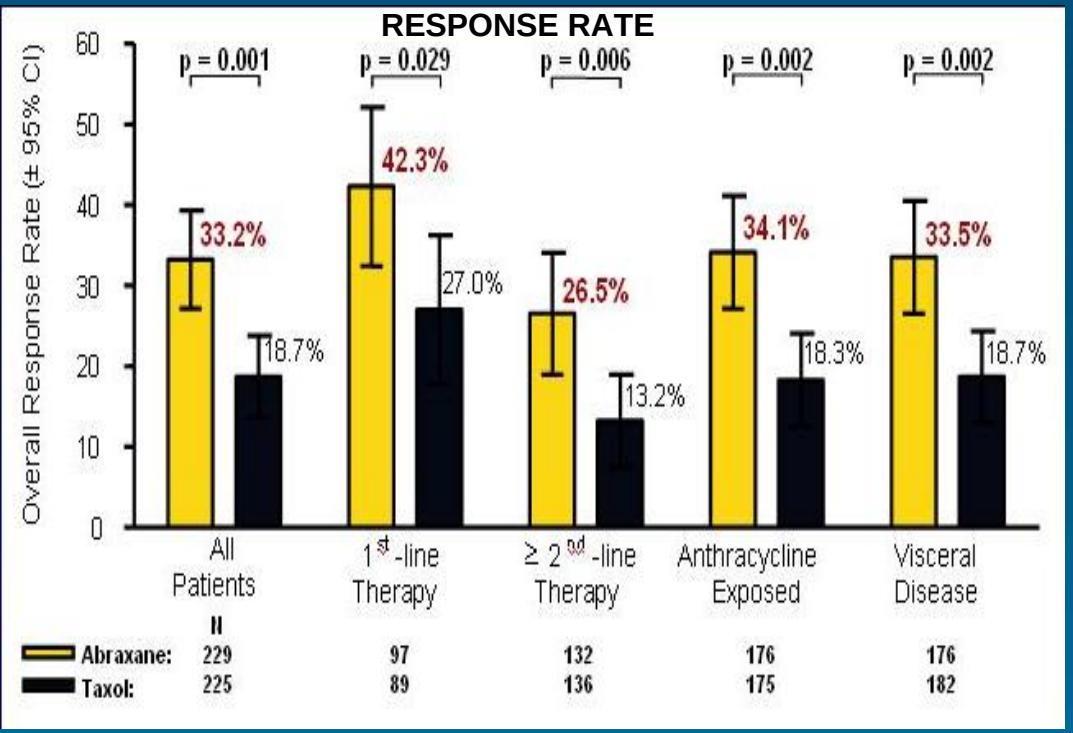
Courtesy Ibrahim et al; MDACC

Phase III Trial : Abraxane vs Taxol
Metastatic Breast Cancer (460 patients)

Randomize (1:1)
N = 460

ABRAXANE® 260 mg/m²
IV over 30 min q 3 wk
No Standard Premedication

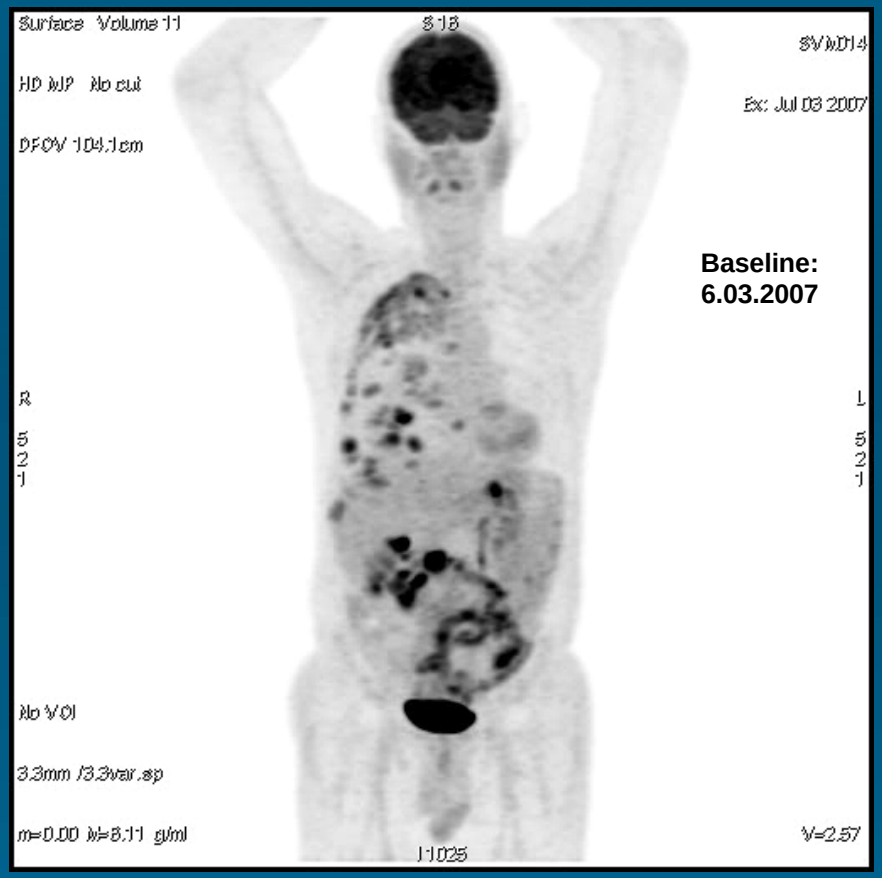
TAXOL® 175 mg/m²
IV over 3 hrs q 3 wk
Premed. with Dexamethasone and Anti-histamines



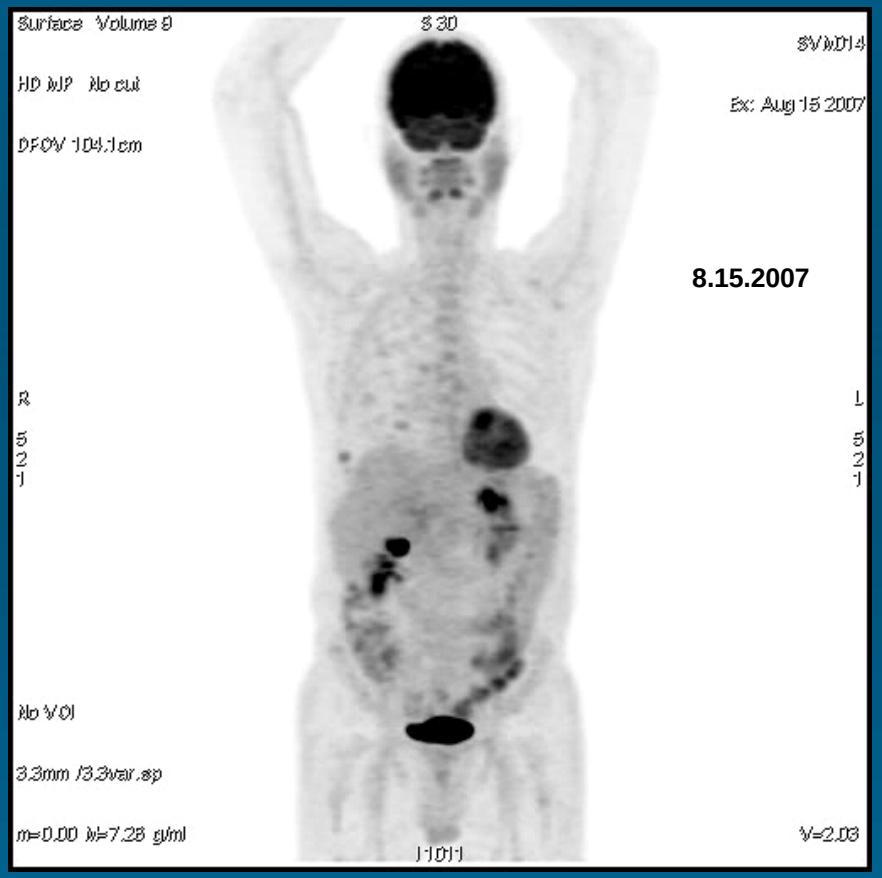
- Significantly improved response rate : 33 vs 19%, p=0.001
- Increased time to tumor progression : 22.7 wk vs 16.6 wk, p=0.003
- Prolonged survival in > 1st line patients : 56.4 weeks vs 46.7 weeks, p = 0.016
- Approved by US FDA in January 2005 for metastatic breast cancer

Gradishar, W. et al - *J Clin Oncol* 23:7794-7803 (2005)

Phase I/II: PET Response in Pancreatic Cancer



Baseline: 6.03.2007

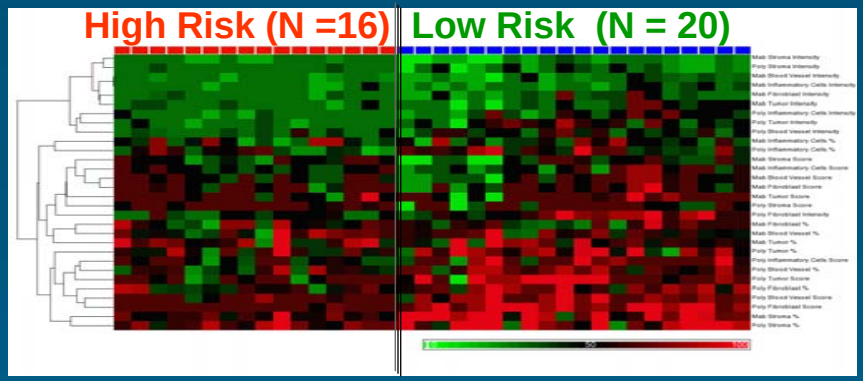


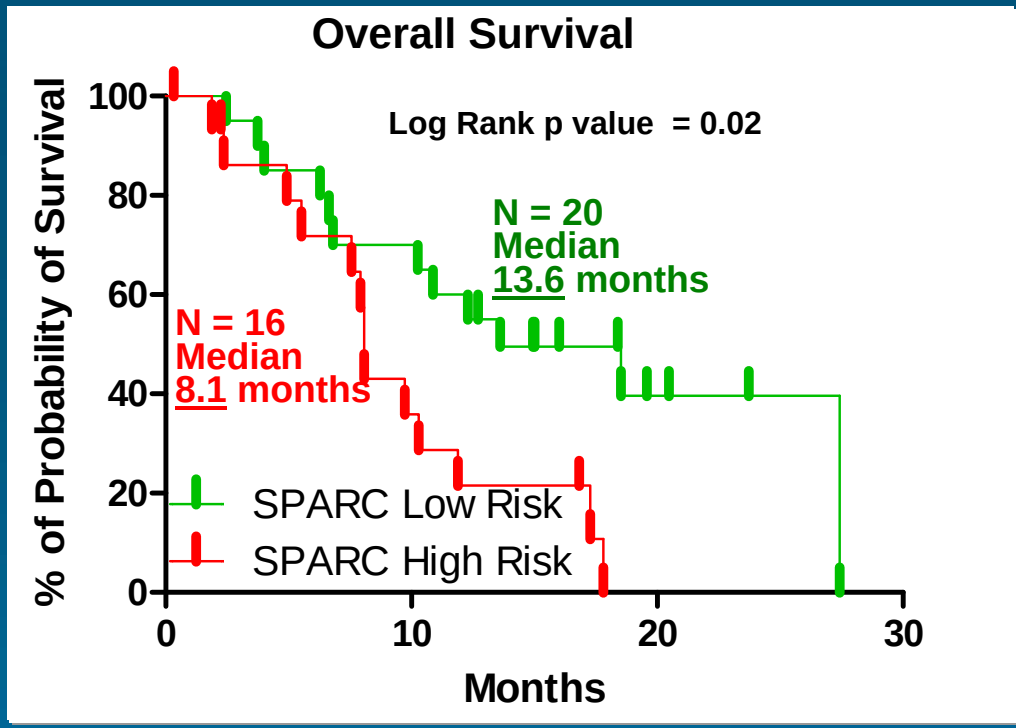
8.15.2007

- paclitaxel (Taxol) is not used in pancreatic cancer
- *nab*-paclitaxel shows remarkable responses

nab-paclitaxel and Pancreatic Cancer : Correlation of the biomarker SPARC and Survival

- SPARC status by IHC was available for 36 patients.
- SPARC signature separated patients into 2 groups
- Survival was correlated to SPARC signature

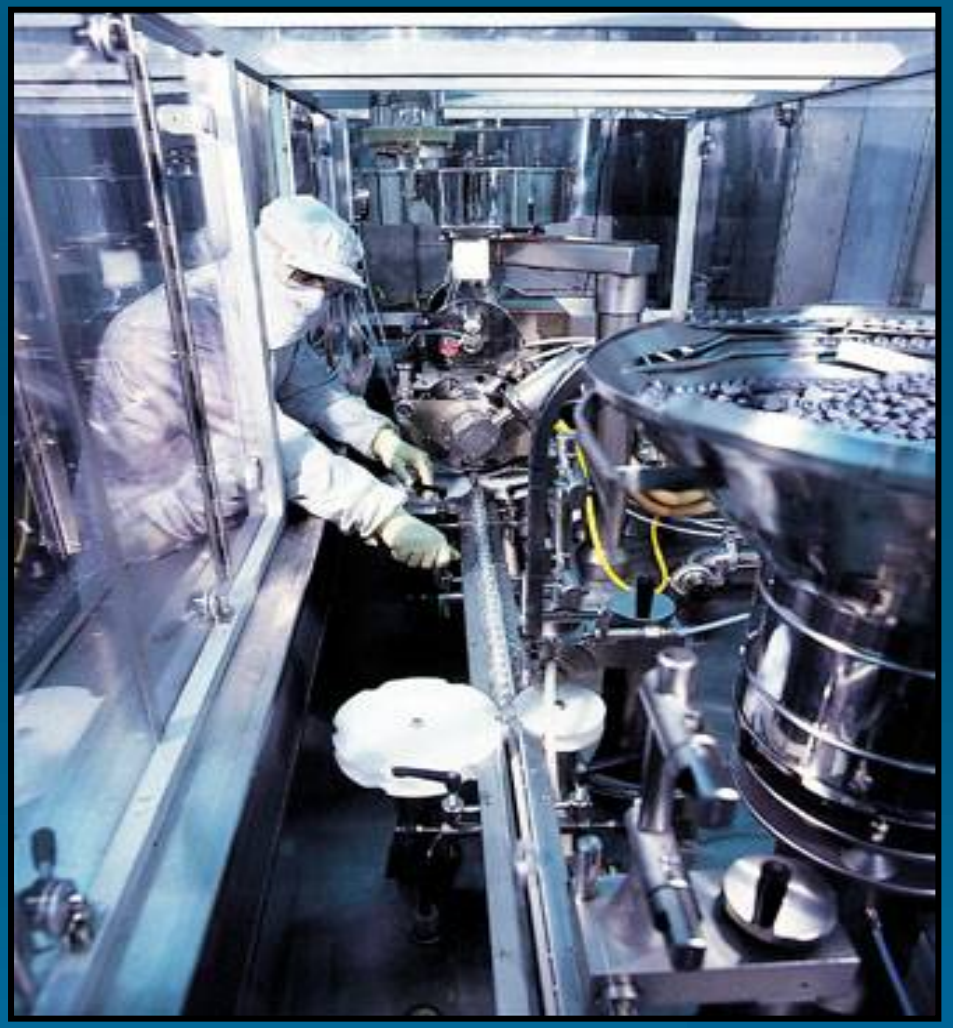




Von Hoff et al, AACR 2010

Commercial Scale Injectable Nanoparticle Manufacturing

- Non-standard equipment / processing
- Innovators are the experts
- Need to work with FDA to enable understanding of technology
- Identify key characteristics of the product and process ranges
- Key issues: consistency and reproducibility
- Appropriate in-process controls and finished product tests
- Our experience with FDA was very positive



Definitions of Nanotechnology adopted by FDA

- FDA has not established its own formal definition ..Our understanding is that the FDA currently relies on the NNI definition.

- National Nanotechnology Initiative (NNI):
  - Nanotechnology is the understanding and control of matter at dimensions of roughly 1 to 100 nanometers, where unique phenomena enable novel applications. ….

- NCI Cancer Nanotechnology Plan (July 2004):
  - Nanotechnology refers to the interactions of cellular and molecular components and engineered materials ….. Such nanoscale objects - typically, though not exclusively, with dimensions smaller than 100 nanometers ……

Nomenclature and labeling of *nab*-paclitaxel : US vs Canada / Europe / Australia

- Appropriate descriptive terms should be allowed in the label/package insert so that clinicians and patients can make an informed decision
  - e.g.: 'Nanoparticle'

- US label:
  - "ABRAXANE for Injectable Suspension (paclitaxel protein-bound *particles* for injectable suspension) is an albumin-bound form of paclitaxel with a mean particle size of approximately 130 nanometers."
  - US FDA ***did not*** permit the use of the word '*nanoparticle*' !
  - FDA used the definition of nanotechnology as <100 nm

- Canadian, EU, Australian label:
  - The term *nanoparticle*, albumin-bound paclitaxel, is used to describe the product