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)

![Diagram of human albumin with a hydrophobic drug, size: ~50-150 nm]
Decreased Toxicity ($LD_{50}$) of nab-paclitaxel vs cremophor-paclitaxel

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

**Taxol**
- Supplied As
  - Paclitaxel 6 mg/ml
  - Cremophor 537 mg/ml
  - Ethanol 396 mg/ml

**nab-paclitaxel vs Cremophor-paclitaxel**

![Graph showing LD50 comparison]

**Table:**

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<thead>
<tr>
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<th>LD$_{50}$ Mice</th>
<th>Human MTD</th>
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<tbody>
<tr>
<td>Cremo-paclitaxel</td>
<td>30.0 mg/kg</td>
<td>175 mg/m²</td>
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<tr>
<td>Nab-paclitaxel</td>
<td>47.0 mg/kg</td>
<td>300 mg/m²</td>
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Characterization of Abraxane (\textit{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

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

Through Two Postulated Mechanisms of Action

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

Diagram:

- Albumin
- Paclitaxel
- Mean size 130 nm
- Injection into circulation
- Dissociation into individual albumin-bound paclitaxel complexes at concentration below threshold
- Albumin-paclitaxel complex
- gp60 receptors
- Caveolae and vesicles
- Albumin-paclitaxel accumulation with SPARC binding
- Tumor blood vessel endothelial cells
- Tumor interstitium
- Paclitaxel-induced tumor cell apoptosis
- Tumor cells
- SPARC

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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 \((p<0.0001)\)

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 treatment

Patient responded to Abraxane treatment

Courtesy Ibrahim et al; MDACC
Phase III Trial: Abraxane vs Taxol
Metastatic Breast Cancer (460 patients)

- **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

Randomize (1:1)
N = 460

- 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

Phase I/II: PET Response in Pancreatic Cancer

- 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