APPLICATION OF NANOTECHNOLOGY TO MEDICINE:
RECENT DEVELOPMENTS, CHALLENGES AND PERSPECTIVES

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NANOSAFE 2016
**Nanotechnology:** design, characterization, production and application of structures, devices and systems by controlling shape and size at the nanometer scale

**Nanomedicine:** application of nanoscale systems to medicine in the screening, diagnosis and treatment of diseases (few nm to < 1000 nm in diameter)
NANOMEDICINE POTENTIAL

Traditional Chemotherapy

- Instability/metabolization
- Limited transmembrane penetration and intracellular accumulation (low availability)
- Lack of cell/tissue specificity (limited activity + toxicity)
- Induction of resistance phenomena

Nanomedicines

- Drug delivery
  - Protection from degradation
  - Increase intracellular penetration
  - Cell/tissue targeting
  - Overcome resistance
  - Higher therapeutic index

Diagnosis
- Increased sensitivity
- Faster disease detection

Nanotheranostic
- Combine therapy and imaging
Established Nanomedicines

- Lipid-based
  - Liposomes
  - Solid Lipid NPs

- Polymer-based
  - Micelles
  - Dendrimers
  - Nanoparticles

Drug Conjugates
- Antibody-drug conjugate
- Polymer-drug conjugate

Inorganic NPs
- Silica NPs
- Iron oxide NPs
- Hafnium oxide NPs

Viral particles

Emergence of new treatments with improved specificity

1st generation

Biodegradable/biocompatible

Drug

2nd generation

• Biodegradable/biocompatible
• Stealth
• Long circulating

3rd generation

• Biodegradable/biocompatible
• Stealth
• Targeted/functionalized

NANOTECHNOLOGY IN DRUG DELIVERY
Combine targeted therapeutic and diagnostic functions

- Non invasive longitudinal monitoring
- Assessment of disease progression
- Evaluation of intervention efficacy at an early stage

Optimized and individualized treatment protocols
The enhanced permeability and retention effect (EPR)

Enhanced permeability:
- Stimulation of the blood vessel production
- Important vascularization (blood supply)
- Wide fenestrations, abnormal architectures

Enhanced retention:
- Lack of lymphatic drainage

Accumulation in tumor tissues
**NANOTECHNOLOGY IN DRUG DELIVERY**

**Ligand-mediated “active” Targeting**

- **Small molecules**
  - Folic acid
  - Curcumin
- **Peptides/proteins**
  - RGD peptides
  - GRGDS
  - CRGD KGPDC
  - Cyclo(RGDFFK)
- **Carbohydrates**
  - Galactose
  - Hyaluronan
- **Antibodies**
  - EGF
- **Transferrin**

*Nicolas J, Mura S, Brambilla D, Mackiewicz N, Couvreur P. Chem. Soc. Rev. 2013, 42, 1147*
NANOMEDICINE DEVELOPMENT PIPELINE

Bench → Bedside

7 to 20 Years

PRECLINICAL RESEARCH

Formulation → In vitro studies → In vivo studies

CLINICAL INVESTIGATION

Phase I Phase II Phase III

1 to 7 Years

COMMERCIALIZATION

Commercial products
First nanomedicine FDA approved (1995)

Indicated for the treatment of patients with AIDS-related Kaposi's sarcoma, breast cancer and ovarian cancer.

80-90 nm PEG-coated unilamellar liposomes

**Pharmacokinetic parameters**

- **Doxil**
- **Doxorubicin**

![Graph showing pharmacokinetic parameters for Doxil and Doxorubicin](image.png)
First nanomedicine FDA approved (1995)

Indicated for the treatment of patients with AIDS-related Kaposi's sarcoma, breast cancer and ovarian cancer

80-90 nm PEG-coated unilamellar liposomes

Pharmacokinetic parameters

Doxorubicin levels in KS lesions
Dramatic reduction of Cardiotoxicity

0.8% withdrawal due to cardiotoxicity
Increasing of the dose and the duration of the treatment

Palmar-Plantar Erythrodysesthesia (PPE) grading and management

<table>
<thead>
<tr>
<th>Grade</th>
<th>Symptoms</th>
<th>Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>Mild erythema</td>
<td>Redose unless previous grade III or IV</td>
</tr>
<tr>
<td>Grade II</td>
<td>Erythema with desquamation</td>
<td>Delay 1-2 weeks or until resolved to grade 0-1</td>
</tr>
<tr>
<td>Grade III</td>
<td>Blistering</td>
<td>Delay 1-2 weeks or until resolved to grade 0-1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Then redose at 75%</td>
</tr>
<tr>
<td>Grade IV</td>
<td>Diffuse</td>
<td>As for Grade III</td>
</tr>
</tbody>
</table>

Complement activation –related pseudo allergy

Slowing the infusion rate
pretreatment

Working et al., JPET, 1999, 289: 1128
**Nanoparticle albumin-bound (nab) technology**

*Indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy.*

Approved in 41 countries
**NANOMEDICINE IN THE CLINIC**

**ABRAXANE**

**Nanoparticle albumin-bound (nab) technology**

*Indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy.*

Approved in 41 countries

**TAXOL**
- Ethanol/Cremophor-EL
- Allergic, hypersensitivity and anaphylactic reactions peripheral neuropathy
- Drug sequestration by cremophor micelles
- 3h infusion
- Non-linear, less-predictable PK

<table>
<thead>
<tr>
<th>Dose (mg/m²)</th>
<th>Cmax (ng/ml)</th>
<th>AUC (ng·hr/ml)</th>
<th>CL (L/h/m²)</th>
<th>% δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>135</td>
<td>3071</td>
<td>8604</td>
<td>15.9</td>
<td>----</td>
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<tr>
<td>175</td>
<td>5202</td>
<td>15048</td>
<td>11.6</td>
<td>25</td>
</tr>
</tbody>
</table>

**ABRAXANE**
- No premedication
- Cremophor free
- Shorter infusion time (30 min)
- Linear, predictable PK

- LD50 Mice 47.0 mg/kg
- Human MTD 300mg/m²

• LD50 Mice 30.0 mg/kg
• Human MTD 175 mg/m²
How does it work?

1. Receptor-mediated transport (transcytosis) by gp60/caveolae receptors
2. Binding of albumin-drug complex by SPARC in tumor
**Application to pancreatic cancer**

Paclitaxel (Taxol) is not used in pancreatic cancer. Nab-paclitaxel shows remarkable responses: survival correlated to SPARC signature.

**Combination with Gemcitabine: Preclinical Study**

The protein SPARC actively binds the albumin in nab-paclitaxel and further concentrates the drug in the tumor.

Nab-paclitaxel treatment depletes the stroma, collapsing it and bringing tumor cells closer to each other and to blood vessels. As a result, more gemcitabine reaches the cancer cells in the tumor.

![Graph showing intratumor concentration of gemcitabine alone and nab-paclitaxel + gemcitabine.](image)

![Images of collagen type 1 fibers in a gemcitabine-resistant human pancreatic cancer xenograft.](image)

Combination with gemcitabine: Phase III study

861 patients with metastatic pancreatic cancer

<table>
<thead>
<tr>
<th></th>
<th>Nab-Ptx+ Gemcitabine</th>
<th>Gemcitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median overall survival (months)</td>
<td>8.5</td>
<td>6.7</td>
</tr>
<tr>
<td>Patients alive (%) after 1yr</td>
<td>35</td>
<td>22</td>
</tr>
<tr>
<td>Patients alive (%) after 2yr</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Median progression free survival (months)</td>
<td>5.5</td>
<td>3.7</td>
</tr>
<tr>
<td>Tumor response rate (%)</td>
<td>23</td>
<td>7</td>
</tr>
</tbody>
</table>

Nab-paclitaxel+ gemcitabine was generally well tolerated and demonstrated clinical activity in patients with metastatic pancreatic cancer.

MTD established as 125 mg/m² nab-paclitaxel + 1000 mg/m² gemcitabine QW 3/4

SPARC positivity (in stroma) was a significant independent predictor of OS (p=0.041) in nab-paclitaxel + gemcitabine-treated patient.
**NanoTherm™ therapy**
injection of iron oxide nanoparticles directly into the tumor at the beginning of the treatment

**Nanoplan®**
Distribution of nanoparticles
Estimate treatment temperature and magnetic field strength required

**NanoActivator®**
generation of an alternating magnetic field
Change of polarity 100,000 times per second:
activation of NPs and the electromagnetic energy is transformed into heat directly within the tumor tissue

① Direct destruction of tumor cells or sensitization for additional chemotherapy or radiation treatment.
② Possibility of repeated treatments and multimodal therapy concepts.
NanoTherm™ therapy

Aminosilane coated iron oxide NPs

NanoTherm™ therapy: injection of iron oxide nanoparticles directly into the tumor at the start of treatment.

Change of polarity 100,000 times per second: activation of NPs and transformation of electromagnetic energy into heat directly within the tumor tissue.

NanoTherm®

Distribution of nanoparticles

Estimate treatment temperature and magnetic field strength required.

NanoActivator®

Generation of an alternating magnetic field

Clinical applications:
① Direct destruction of tumor cells or sensitization for additional chemotherapy or radiation treatment.
② Possibility of repeated treatments and multimodal therapy concepts.

NanoTherm®, NanoPlan®, NanoActivator®

ANOMEDICINE IN THE CLINIC

**Survival benefit of NanoTherm® therapy**

In combination with stereotactic radiotherapy in 59 patients with recurrent glioblastoma.

<table>
<thead>
<tr>
<th></th>
<th>Median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>After diagnosis of first tumor recurrence</td>
<td>6.2 (13.4)</td>
</tr>
<tr>
<td>After diagnosis of primary tumor</td>
<td>14.6 (23.2)</td>
</tr>
</tbody>
</table>

**ANOMEDICINE®**

THE NANOMEDICINE COMPANY

**magforce®**
Glioblastoma multiforme

NanoTherm™ therapy centers in Germany

NEW TRIAL: MF1001

Open-label, randomized, controlled study to determine the efficacy and safety of NanoTherm® monotherapy and NanoTherm® in combination with radiotherapy versus radiotherapy alone in recurrent / progressive glioblastoma.

Patient enrolment has started in the first quarter of 2014.
Target size 309 patients

<table>
<thead>
<tr>
<th>Primary EndPoint:</th>
<th>Survival rate 12 months after the start of the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary EndPoints:</td>
<td>Overall Survival, progression-free survival, Safety, quality of life</td>
</tr>
</tbody>
</table>

Expansion to the US: treatment of glioblastoma and prostate cancer
The long road of R&D

1st state of testing in humans

How well does the drug work?

Comparison with current gold standard treatment

« Real life » patients

Promising in Clinical trials
**Livatag®: Doxorubicin Transdrug**

**Nanoparticle formulation of doxorubicin**

**Polymer network:** poly (isohexyl cyanoacrylate)

Nanoparticle size: 100-300 nm

Solvent free

Reconstitution before administration

Parental administration

**10 mg eq.doxorubicin/vial**

**Overcome tumor multidrug resistance**

**Doxorubicin Transdrug**
**Livatag®: Doxorubicin Transdrug**

**Nanoparticle formulation of doxorubicin**

**Polymer network:** poly (isoheptyl cyanoacrylate)
Nanoparticle size: 100-300 nm
Solvent free
Reconstitution before administration
Parental administration

10 mg eq.doxorubicin/vial

**SEM image**

**Overcome tumor multidrug resistance**

**PRECLINICAL STUDIES**

In vivo antitumor cytotoxicity of PIHCA-Dox vs Dox on HCC arising in X/myc transgenic mice

Reversion of chemo-resistance and enhanced cytotoxicity compared to free doxorubicin on resistant human hepatoma and metastatic liver cells

Potential significant breakthrough in the treatment of hepatocellular carcinoma

Barraud et al., | Hepatology, 2005, 42: 736
**Clinical studies**

**Phase II**

**Baseline**

- **Tumor size 3000 mm²**

**Intra-arterial infusion**

- **(30 mg/m²)**

**After 4 weeks**

- **Evident necrotic area**

**Increased survival time** of patients suffering from hepatocellular carcinoma by **17 months**, as compared with 15 months for patients getting current best of care (TACE transarterial chemoembolisation with a cytotoxic drug).
ReLIVE: international phase III clinical study  NCT01655693

Phase III: 400 patients with advanced stage hepatocellular carcinoma, after failure or intolerance to Sorafenib

Randomized, open label, comparative 3 parallel arms study.
Administration through a slow 6 hours IV infusion every 4 weeks.

20 mg/m² every 4 weeks
30 mg/m² every 4 weeks
Best Standard Care

Until progression Or Toxicity

Endpoints
Primary: OS
Secondary: Response rate and progression-free / Pharmacokinetic in selected sites

Fast Track status (accelerated review procedure) from the FDA

Data Safety Monitoring Board
An independent DSMB blindly reviews safety data every 6 months. Since the beginning of the clinical trial, around 375 prolonged IV infusion of DT were administered and didn’t show pulmonary toxicity. Six DSMB meetings occurred leading to continue the trial without modification.

Preliminary outcomes of the phase III by 2017
Stimuli Responsive

ThermoDox

Heat-activated doxorubicin loaded Liposomes

“Leaky” Tumor Blood Vessels
Heat Adds Permeability
Heat-Triggered, Mechanical Release

In Vivo
After 1 hour at 42°C, heat-sensitive formulation delivered most drugs to tumor.

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>RESEARCH</th>
<th>PRE-CLINICAL</th>
<th>PHASES 1-2</th>
<th>PHASE 3</th>
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<tbody>
<tr>
<td>Primary Liver</td>
<td>ThermoDox®/OPTIMA Study</td>
<td>Phase III enrolling</td>
<td></td>
<td></td>
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<tr>
<td>RCW Breast</td>
<td>ThermoDox/DIGNITY Study</td>
<td>Phase II enrolling</td>
<td></td>
<td></td>
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<tr>
<td>Liver</td>
<td>ThermoDox+HIFU/TARDOX Study</td>
<td>Phase II with Oxford University</td>
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<tr>
<td>Glioblastoma</td>
<td>ThermoDox+HIFU</td>
<td>Research Collaboration with Brigham &amp; Women’s Hospital and Harvard Medical School</td>
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<tr>
<td>Breast</td>
<td>ThermoDox+HIFU</td>
<td>Phase II Planned</td>
<td></td>
<td></td>
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<tr>
<td>Pancreatic</td>
<td>ThermoDox+HIFU</td>
<td>Focused Ultrasound Foundation co-sponsored with University of Washington</td>
<td></td>
<td></td>
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</tbody>
</table>
Micro-metastasis outside the ablation zone “kill” area. Potential site of recurrence if not treated.

**ThermoDox + RFA:**
- Infuse ThermoDox ~15 minutes prior to RFA
- Drug concentrates in the “Thermal Zone”
- Ablation releases doxorubicin in “Thermal Zone” expanding treatment area and destroying micro-metastases

Ablated Tumor and 1 cm “Tumor-Free” Margin

- ThermoDox
- Ablation Zone
- Thermal Zone

50°C < T < 39°C
Micro-metastasis outside the ablation zone “kill” area. Potential site of recurrence if not treated.

**Ablated Tumor and 1 cm “Tumor-Free” Margin**

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**Phase III HEAT Hepatocellular Carcinoma Study of RFA and ThermoDox® Study**

**Primary EndPoint:** Progression Free Survival

**Secondary EndPoints:** Overall Survival, Time to local Recurrence, time to Definite Worsening, Safety
Micro-metastasis outside the ablation zone “kill” area. Potential site of recurrence if not treated

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Phase III HEAT Hepatocellular Carcinoma Study of RFA and ThermoDox® Study

Primary Endpoint: Progression Free Survival

Secondary Endpoints: Overall Survival, Time to local Recurrence, time to Definite Worsening, Safety

Phase III OPTIMA Study: based on sub-group analysis from the HEAT study.
Micro-metastasis outside the ablation zone “kill” area. Potential site of recurrence if not treated

**Ablated Tumor and 1 cm “Tumor-Free” Margin**

- **ThermoDox + RFA:**
  - Infuse ThermoDox ~15 minutes prior to RFA
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**Phase III HEAT Hepatocellular Carcinoma Study of RFA and ThermoDox® Study**

- **Primary EndPoint:** Progression Free Survival
- **Secondary EndPoints:** Overall Survival, Time to local Recurrence, time to Definite Worsening, Safety

**Phase III OPTIMA Study**

- Optimized RFA standardized to a minimum of 45 minutes to treat lesions 3 to 7 cm
- **Primary EndPoint:** Overall Survival
Phase III OPTIMA Study

ThermoDox plus RFA ≥45 minutes vs RFA alone ≥45 minutes. Single lesions 3 to 7 cm

Primary Endpoint: Overall Survival

2.1-year improvement in OS in patients with single lesions
Faculty of Pharmacy

Institut Galien Paris-Sud
UMR CNRS 8612

Pr Patrick Couvreur’s team: Nanomedicine for treatment of severe diseases
Cancer M109 and MCF7 cells

Aβ_{1-42} peptide and fibrils

Rhodamine B

Vitamin B7

Curuminoids

M109 and MCF7 cells

Concomitant self-assembly

EASY TO FUNCTIONALIZE POLYMER NPs

Brambilla D. et al., Chem. Comm., 2010, 46, 2602
Le Droumaguet et al., ACS Nano, 2012, 6, 5866
Chemically conjugation of squalene to a biologically active drug molecule leading to bioconjugates which self-assemble as nanoparticles in water.

Squalene (SQ)

- Maksimenko et al., PNAS 2014
- Reddy et al., Drug Met. Displ., 2008
- Couvreur et al., Small, 2008
- Caron et al., Adv. Healthc Mater. 2013
- Raouane et al., Thyroid 2013
- Sémiramoith, et al., ACS Nano 2012
- Caron et al., PCT/FR2011/052914
- Caron et al., PCT/FR2012/12 52382
- Maksimenko et al., ACS Nano 2014
- Gaudin et al., Nature Nanotech. 2014
- Couvreur et al., PCT/FR2012/12 52382
Specific ligand for pancreatic tumor targeting

In vivo phage display screening on RIP1-Tag2 transgenic model of islet cell carcinoma

Identification of molecular markers accessible via the circulation

Angiogenic islets or tumor-homing peptides

Abundant localization in RIP1-Tag2 tumors but little or no localization in angiogenic islets or normal islets

Joyce JA, et al., Cancer Cell 2003 Nov. 4:393
**In vivo targeting and therapeutic efficacy**

- Superior activity of SQ-based NPs compared to the free drug
- Functionalized NPs impair tumor growth more efficiently and increase the apoptotic rate
- Increase in apoptosis also in tumor blood vessels

**Angiogenic vessel area**

- Reduction of angiogenic vessels area and increase of pericyte coverage

**Pericyte coverage**

*Hallmarks of tumor blood vessels normalization*

Valetti S, et al., JCR, 2014, 192, 29
SQGem NPs

Cytotoxic Drug + Squalene → Vascular disrupting agent

SQGem NPs

SQGem/isoCA-4 nanocomposites

SQGem NPs

SQGem/isoCA-4 NPs
A new long circulating non PEGylated nanomedicine

[Chemical structure of SQDoxo NPs]

Extended by the blood flow along streamlines

**Pharmacokinetic**

Plasma Doxorubicin (µM)

- SQ-Dox NAs
- Doxorubicin

Heart Doxorubicin (%ID g⁻¹)

- Dox
- SQ-Dox NAs

Urine Doxorubicin (µg)

- Dox
- SQ-Dox NAs

Tumor Doxorubicin (%ID g⁻¹)

- Dox
- SQ-Dox NAs

**MiaPaca2: SQ vs commercial formulations**

Tumor Volume (mm³)

- Doxorubicin
- SQ-Dox NAs
- Hyocin
- Saline 0.9%
- Cefaly

Relative Body Weight Change (%)

- Doxorubicin
- SQ-Dox NAs
- Hyocin
- Saline 0.9%
- Cefaly

SQADENOSINE NPs

✓ important role in energetic metabolism (ATP) and in signal transduction (AMPc)
✓ neurotransmitter and neuromodulator
✓ pharmacological efficacy in several neurological disorders

✗ rapidly metabolized after intravenous injection
✗ does not cross the BBB

Cerebral ischemia model

Spinal cord injury model

Pharmacological activity in an model of spinal cord injury

Complete paralysis

Complete recovery of the hind limbs

Step with plantar weight support

Keep the tail consistently up

## Web of Science (01 November 2016)

<table>
<thead>
<tr>
<th>Published articles</th>
<th>Liposomes &amp; cancer</th>
<th>Nanoparticles &amp; cancer</th>
<th>Micelles &amp; cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>7028</td>
<td>30676</td>
<td>5354</td>
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## Clinicaltrials.gov

<table>
<thead>
<tr>
<th>Total</th>
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<tbody>
<tr>
<td>Liposomes</td>
<td>1895</td>
<td>476</td>
</tr>
<tr>
<td>Nanoparticles</td>
<td>244</td>
<td>94</td>
</tr>
<tr>
<td>Micelles</td>
<td>29</td>
<td>10</td>
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</table>

## Cancer related

<table>
<thead>
<tr>
<th>Total</th>
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<tbody>
<tr>
<td>Liposomes</td>
<td>1608 (85%)</td>
<td>398</td>
</tr>
<tr>
<td>Nanoparticles</td>
<td>174 (71%)</td>
<td>66</td>
</tr>
<tr>
<td>Micelles</td>
<td>15 (52%)</td>
<td>7</td>
</tr>
</tbody>
</table>
**Prostate specific membrane antigen (PSMA)-targeted nanomedicines**

- **BIND-014** (PSMA-targeted docetaxel)
- **BING-510** PSMA-targeted vincristine
- **PLK1, KSP inhibitor accurins**

**Patents Expressing PSMA**

<table>
<thead>
<tr>
<th>TUMOR</th>
<th>TUMOR CELLS</th>
<th>NEOVASCULATURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>184/184 (100%)</td>
<td>2/12 (17%)</td>
</tr>
<tr>
<td>Breast</td>
<td>0/6 (0%)</td>
<td>5/6 (83%)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>0/130 (0%)</td>
<td>110/130 (85%)</td>
</tr>
<tr>
<td>Renal Cell</td>
<td>0/75 (0%)</td>
<td>67/75 (89%)</td>
</tr>
<tr>
<td>Bladder</td>
<td>8/167 (5%)</td>
<td>167/167 (99%)</td>
</tr>
<tr>
<td>Gastric</td>
<td>0/119 (0%)</td>
<td>79/119 (66%)</td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>0/5 (0%)</td>
<td>5/5 (100%)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>0/5 (0%)</td>
<td>5/5 (100%)</td>
</tr>
<tr>
<td>Pancreatic Duct</td>
<td>0/4 (0%)</td>
<td>4/4 (100%)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>0/5 (0%)</td>
<td>5/5 (100%)</td>
</tr>
<tr>
<td>Soft Tissue Sarcoma</td>
<td>0/6 (0%)</td>
<td>5/6 (83%)</td>
</tr>
</tbody>
</table>

**PSMA is not found in normal vasculature**
Targeting of the prostate specific membrane antigen (PSMA)

SPECT imaging of $^{111}$In-labeled PSMA-targeted nanoparticles in PSMA-positive and negative prostate tumor xenografts
Targeting of the prostate specific membrane antigen (PSMA)

SPECT imaging of $^{111}$In-labeled PSMA-targeted nanoparticles in PSMA-positive and negative prostate tumor xenografts

Early tests in animals and small clinical trials showed that the approach was safer than docetaxel alone.

Later clinical trials disappointed.
- BIND-014 failed against cervical and head-and-neck cancers
- Efficacy on lung cancer was not clear
<table>
<thead>
<tr>
<th>Rank</th>
<th>Status</th>
<th>Study</th>
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<tbody>
<tr>
<td>1</td>
<td>Completed</td>
<td>A Phase 2 Study to Determine the Safety and Efficacy of BIND-014 (Docetaxel Nanoparticles for Injectable Suspension), Administered to Patients With Metastatic Castration-Resistant Prostate Cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conditions: CRPC, Prostate Cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intervention: Drug: BIND-014</td>
</tr>
<tr>
<td>2</td>
<td>Completed</td>
<td>A Study of BIND-014 Given to Patients With Advanced or Metastatic Cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conditions: Metastatic Cancer, Cancer, Solid Tumors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intervention: Drug: BIND-014</td>
</tr>
<tr>
<td>3</td>
<td>Completed</td>
<td>A Phase 2 Study to Determine the Safety and Efficacy of BIND-014 (Docetaxel Nanoparticles for Injectable Suspension) as Second-line Therapy to Patients With Non-Small Cell Lung Cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Condition: Non-small Cell Lung Cancer</td>
</tr>
<tr>
<td></td>
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<td>Intervention: Drug: BIND-014</td>
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<td>4</td>
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<td>A Study of BIND-014 (Docetaxel Nanoparticles for Injectable Suspension) as Second-line Therapy for Patients With KRAS Positive or Squamous Cell Non-Small Cell Lung Cancer</td>
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<td>Conditions: KRAS Positive Patients With Non-small Cell Lung Cancer; Squamous Cell Non-small Cell Lung Cancer</td>
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<td>Intervention: Drug: BIND-014 (Docetaxel Nanoparticles for Injectable Suspension)</td>
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<td>Terminated</td>
<td>A Study of BIND-014 in Patients With Urothelial Carcinoma, Cholangiocarcinoma, Cervical Cancer and Squamous Cell Carcinoma of the Head and Neck</td>
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<td>Conditions: Urothelial Carcinoma, Cholangiocarcinoma, Cervical Cancer, Squamous Cell Carcinoma of Head and Neck</td>
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<td>Intervention: Drug: BIND-014 (docetaxel nanoparticles for injectable suspension)</td>
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ACCURINS (BIND-014 CLINICAL TRIALS)

TROUBLED TIMES
BIND Therapeutics raised US$70.5 million in an initial public offering of stock in September 2013. But the company’s stock price has fallen in response to its recent financial woes.

15 March: BIND sets out new research strategy
6 April: BIND announces that it will end one of its BIND-014 clinical trials early
2 May: Firm declares bankruptcy

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People are not interested in funding technology right now. They're interested in funding later-stage projects. And the one at this company didn't have what it takes.

You should eventually be able to personalize the nanoparticles to the need,” he says. “It’s just that we’re not even close to there yet.

Companies should determine whether a nanoparticle would penetrate a patient’s tumor before administering the therapy.
So many drug delivery systems on the paper: so few drugs. Why?

The efficacy in preclinical studies can be incredible: the difference seems to collapse to nearly zero in human tumors. 95% failure rate for anticancer drugs after entering in clinical trials.

Failure during efficacy phase study (millions of dollars are lost)

- Attempt of accumulation at level of the tumor via EPR effect
- Attach ligands which can participate in ligand binding events
- Use of animal models significantly different from their naturally-derived counterpart
- Laboratory vs clinic: Benchmark and endpoints are different (tumor volume, reference treatment)
- Patient to patient and tumor to tumor heterogeneity

Great progresses occurred

Drug carriers have been approved and saved/improved the quality of countless lives
# Bench to Bedside Translation

## Scientific challenges

- Physico-chemical and biological evaluation
- Batch to batch analysis
- Characterization under clinically relevant conditions
- Interactions with biological systems
- Impact on the immune system

## Regulatory challenges

- Clear definition of nanomedicines
- Guidelines and standards for the manufacturing processes and quality assessment
- Characterization and quality control of nanosimilars
- Expertise of regulators
- Risk characterization

## Toxicsology

- Nanosized materials behave differently to low MW drugs
- Fate of nanoparticles and metabolic products
- Lack of exposure information
- Lack of hazard information
- Limited studies investigated human health impacts
- Lack of standardised tests to assess safety

## Manufacturing of clinical batches

- From lab to GMP unit
- Scale up of manufacturing processes
- Technical manufacturing challenge
- High cost of development

## Criticism and skepticism

Make publicy available negative data: Not rewarding in academia but useful to understand the faults of the drug/models/protocols
THANKS FOR YOUR ATTENTION