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

Simona MURA
Institut Galien Paris-Sud
UMR CNRS 8612
Université Paris-Sud 11
Châtenay-Malabry
France

simona.mura@u-psud.fr

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NanoItaly 2015
**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
- Dendrimers
- Nanoparticles

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

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

Viral particles

Adapted from Wicki et al., J Control Release 2015, 200: 130
Nanotechnology in drug delivery

Emergence of new treatments with improved specificity

1\textsuperscript{st} generation

- Biodegradable/biocompatible

2\textsuperscript{nd} generation

- Biodegradable/biocompatible
- Stealth
- Long circulating

3\textsuperscript{rd} generation

- Biodegradable/biocompatible
- Stealth
- Targeted/functionalized
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

**Passive Targeting**

*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

**Ligand–Mediated “Active” Targeting**

Small molecules
- Folic acid
- Biotin

Carbohydrates
- Galactose
- Hyaluronan
- Galactose

Antibodies
- RGD peptides
- EGF

Peptides/proteins
- Transferrin
Nanomedicine in the clinic

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

Doxil
Nanomedicine in the clinic

**Doxil**

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>I</td>
<td>Mild erythema</td>
<td>Redose unless previous grade III or IV</td>
</tr>
<tr>
<td>II</td>
<td>Erythema with desquamation</td>
<td>Delay 1-2 weeks or until resolved to grade 0-1</td>
</tr>
<tr>
<td>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>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
Nanomedicine in the clinic

**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

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**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>% δ</th>
<th>AUC (ng·hr/ml)</th>
<th>% δ</th>
<th>CL (L/h/m²)</th>
<th>% δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>135</td>
<td>3071</td>
<td>---</td>
<td>8604</td>
<td>---</td>
<td>15.9</td>
<td>---</td>
</tr>
<tr>
<td>175</td>
<td>5202</td>
<td>70</td>
<td>15048</td>
<td>75</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
**How does it work?**

1. Receptor-mediated transport (transcytosis) by GP60 and caveolae
2. Binding of albumin-drug complex by SPARC in tumor
Paclitaxel (Taxol) is not used in pancreatic cancer
Nab-paclitaxel shows remarkable responses: survival correlated to SPARC signature

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.

Von Hoff et al., J Clin Oncol, 2011, 36, 5742
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>
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</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 start of treatment

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.
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

Source: AGCS
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

SEM image

Overcome tumor multidrug resistance
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

**SEM image**

Overcome tumor multidrug resistance

**Histological counting of apoptotic hepatocytes (%)**

![](image)

Potential significant breakthrough in the treatment of hepatocellular carcinoma

**PRECLINICAL STUDIES**

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

Barraud et al., J Hepatology, 2005, 42: 736
**Livatag®: doxorubicin Transdrug**

**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**

Compare repeated intravenous administration of Livatag® to the transarterial chemoembolisation

Phase III: 400 patients with advanced stage hepatocellular carcinoma, after failure or intolerance to sorafenib (Nexavar®)
July 2015 (50% of patients randomized)

**Fast Track status** (accelerated review procedure) from the FDA
Data Safety and Monitoring Board meeting: absence of unexpected safety signals that could lead to protocol modification or even study stop.

Preliminary outcomes of the phase III by 2017
# Prostate specific membrane antigen (PSMA)-targeted nanomedicines

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

## Target tumor at three levels: tissue, cellular and molecular

- **Stealth and protective layer:** prolonged circulation time
- **Targeting ligands**
- **Controlled-release polymer matrix**
- **Therapeutic payload**

## PATIENTS EXPRESSING PSMA

<table>
<thead>
<tr>
<th>TUMOR</th>
<th>TUMOR CELLS</th>
<th>NEOVASCULATURE</th>
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</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

Accurins (BIND-014 preclinical)

BIND-014 is highly differentiated from, and superior to, Taxotere.
Accurins *(Bind-014 clinical trials)*

<table>
<thead>
<tr>
<th>Proprietary Programs</th>
</tr>
</thead>
</table>
| **BIND-014**  
(PSMA-targeted docetaxel) |
| KRAS-mutated non-small cell lung cancer  
(NSCLC) |
| Squamous histology NSCLC |

**Phase 1**: safety, tolerability, maximum tolerated dose (MTD), and PK of BIND-014 administered once every 21 days  
(non-small cell lung; hepatobiliary; head and neck; prostate and other solid tumors)

Generally **safe** and **well-tolerated** at the MTD of 60 mg/m²  
Pharmacokinetic profile substantially different from PK of docetaxel.  
1 **complete response**, 3 **partial responses** and 5 patients with **stable disease** lasting at least four cycles (> 12 weeks).
**Phase 1:** safety, tolerability, maximum tolerated dose (MTD), and PK of BIND-014 administered once every 21 days (non-small cell lung; hepatobiliary; head and neck; prostate and other solid tumors)

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1 *complete response*, 3 *partial responses* and 5 patients with *stable disease* lasting at least four cycles (> 12 weeks).

**Phase 2:** *Recruiting*  
**iNSITE1 trial:** KRAS mutant or squamous histology NSCLC  
40 patients with advanced metastatic NSCLC: BIND-014 was well tolerated with clinically meaningful anti-tumor activity at a lower dose than conventional docetaxel  
Promising anti-tumor activity in patients with KRAS mutant tumors and patients with squamous cell carcinomas  
Reduction of side effects (neutropenia, anemia, neuropathy, and alopecia)  
**iNSITE2 trial:** urothelial carcinoma, cholangiocarcinoma, cervical cancer, and squamous cell carcinoma of the head and neck
<table>
<thead>
<tr>
<th>Proprietary Programs</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIND-014</td>
<td>safety</td>
<td>安全</td>
<td></td>
</tr>
<tr>
<td>PSMA-targeted docetaxel</td>
<td>tolerability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KRAS-mutated non-small cell lung cancer (NSCLC)</td>
<td>承受</td>
<td></td>
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<tr>
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### Phase 1
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### Phase 2: Recruiting
**iNSITE1 trial**: KRAS mutant or squamous histology NSCLC
- 40 patients with advanced metastatic NSCLC: BIND-014 was well tolerated with clinically meaningful anti-tumor activity at a lower dose than conventional docetaxel
- Promising anti-tumor activity in patients with KRAS mutant tumors and patients with squamous cell carcinomas
- Reduction of side effects (neutropenia, anemia, neuropathy, and alopecia)

**iNSITE2 trial**: urothelial carcinoma, cholangiocarcinoma, cervical cancer, and squamous cell carcinoma of the head and neck

### No evidence of neurotoxicity

<table>
<thead>
<tr>
<th>BIND-S10</th>
<th>(PSMA-targeted vincristine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid tumor Accurin</td>
<td></td>
</tr>
<tr>
<td>Hematologic cancer Accurin</td>
<td></td>
</tr>
</tbody>
</table>

**PLK1, KSP-inhibitor Accurins**
- Multiple PLK1 oncology targets
- Multiple KSP oncology targets
Stimuli responsive

Efficient spatio temporal and dosage release control

Endogenous stimuli
- pH
- Redox status (glutathion concentrations)
- Enzymatic activity

Exogenous stimuli
- Magnetic field
- Electric field
- Light
- Ultrasound
- Temperature

S. Mura, J. Nicolas, P. Couvreur, Nature Materials, 2013, 12, 991
ThermoDox

**Heat-activated doxorubicin loaded Liposomes**

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>
</tr>
</thead>
<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>
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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>
</tr>
<tr>
<td>Pancreatic</td>
<td>ThermoDox+HIFU</td>
<td>Focused Ultrasound Foundation co-sponsored with University of Washington</td>
<td></td>
<td></td>
</tr>
</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
- $50^\circ C < T < 39^\circ C$
Ablated Tumor and 1 cm “Tumor-Free” Margin

Micro-metastasis outside the ablation zone “kill” area. Potential site of recurrence if not treated

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

<table>
<thead>
<tr>
<th>Primary EndPoint:</th>
<th>Progression Free Survival</th>
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**Ablated Tumor and 1 cm “Tumor-Free” Margin**
- ThermoDox
- Ablation Zone
- Thermal Zone

56°C < T < 39°C

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

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Phase III OPTIMA Study

Optimized RFA standardized to a minimum of 45 minutes to treat lesions 3 to 7 cm

**Primary Endpoint:** Overall Survival
Stimuli responsive

ThermoDox

Micro - metastasis outside the ablation zone “kill” area. Potential site of recurrence if not treated

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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

79 months for the ThermoDox® plus optimized RFA group versus 53.6 months for the optimized RFA only group
Nanotechnology in preclinical

Faculty of Pharmacy

Institut Galien Paris-Sud
UMR CNRS 8612

Pr Patrick Couvreur’s team: Nanomedicine for treatment of severe diseases
In our lab easy to functionalize polymer NPs

Cancer

M109 and MCF7 cells

Aβ1-42 peptide and fibrils

Rhodamine B

Vitamin B7

Curcuminoids

Concomitant self-assembly

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

Maksimenko et al., *PNAS* 2014


Couvreur et al., *Small*, 2008

Raouane et al., *Thyroid* 2013

Sémiramothe et al., *ACS Nano* 2012

Gaudin et al., *Nature Nanotech.* 2014

Caron et al., *PCT/FR2011/052914*

Maksimenko et al., *PCT/FR2012/1252382*

Caron et al., *Adv. Healthc Mater.* 2013

Couvreur et al., *PCT/FR2012/122382*
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

CKAAKN Peptide

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
- Increase of pericyte coverage

### Pericyte coverage

- Hallmarks of tumor blood vessels normalization

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**SQGem NPs**

**CKAAKN Peptide-functionalized**

Valetti S, et al., JCR, 2014, 192, 29
A new long circulating non PEGylated nanomedicine

SQDoxorubicin NPs

Extended by the blood flow along streamlines

Pharmacokinetic

MiaPaca2: SQ vs commercial formulations

When shape matters!
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

SQAdenosine NPs

## Clinical trials

**Clinicaltrials.gov**

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Open</th>
<th>Open-Unknown status</th>
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<tbody>
<tr>
<td>Liposomes</td>
<td>1615</td>
<td>420</td>
<td>331</td>
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<tr>
<td>Nanoparticles</td>
<td>204</td>
<td>80</td>
<td>65</td>
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<tr>
<td>Micelles</td>
<td>22</td>
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## Cancer related

<table>
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<tr>
<th></th>
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<tr>
<td>Liposomes</td>
<td>1386 (85%)</td>
<td>346</td>
<td>265</td>
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<tr>
<td>Nanoparticles</td>
<td>153 (75%)</td>
<td>63</td>
<td>54</td>
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<tr>
<td>Micelles</td>
<td>11 (50%)</td>
<td>3</td>
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## Web of Science (10 September 2015)

### Published articles

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The translational gap for nanomedicines

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 counter part
• 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

Criticism and skepticism

Make publicly available negative data: Not rewarding in academia but useful to understand the faults of the drug/models/protocols

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

Toxicology

- 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
THANKS FOR YOUR ATTENTION

http://www.umr-cnrs8612.u-psud.fr/
http://www.erc_ternanomed.u-psud.fr/index.html