NANOMEDICINES ON THE MARKET AND IN DEVELOPMENT: Nanoparticles

Rogério Sá Gaspar
Current positions

- Full Professor, Faculty of Pharmacy University of Lisbon - FFUL (Portugal)
- Coordinator of Nanomedicine & Drug Delivery Systems research group at the Research Institute for Medicines and Pharmaceutical Sciences (iMed.UL), since 2007
- Member of the General Council at the University of Lisbon (Portugal), since 2008
- Member of the Medicines Evaluation Committee at INFARMED and different positions in European regulatory affairs (1995-2002 and since September 2008, Portugal)
- Member of adhoc expert group in nanomedicines at EMA (since April 2009)
- Member of the coordination of MScs in Regulatory Affairs (since 2001), in Advanced Pharmacotechnics (since 2006) and in Pharmaceutical Engineering (since 2007) at FFUL
- Doctoral Programme in BioNanotechnology (University Lisbon, approved 2009, to be started)
- Member of the Executive Committee of EUFEPS since 2009 (liaison with Network in Pharmacogenetics/Pharmacogenomics, chair of Network in Regulation & Science 2010, currently establishing Network in Nanomedicine)
- Controlled Release Society (CRS), Committee in Regulatory Affairs, since 2010
- Member of Board, Portuguese Society for Pharmaceutical Sciences (SPCF) since 2005
• The views and opinions hereby expressed reflect only my personal opinion and not the views of institutions or organisations with which I’m or have been affiliated in the past or present.
Objectives

- Review the current status of medicinal products (nanopharmaceuticals)
- Review the key factors for design in respect of specific medical use
- Describe the key factors for risk-benefit assessment looking at quality, safety and efficacy
- Emerging technologies
- Specific challenges and opportunities
MRI contrast agents

Paramagnetic:
- Gadopentetic acid
- Gadoteric acid
- Gadodiamide
- Gadolinium
- Gadoteridol
- Mangafodipir
- Gadoversetamide
- Ferric ammonium citrate
- Gadobenic acid
- Gadobutrol
- Gadoxetic acid

Superparamagnetic:
- Ferumoxsil
- Ferristene
- Iron oxide, nanoparticles

Nanoparticulate systems:
- Iron oxide nanoparticles coated with carboxydextran (Cliaivist/Resovist, Bayer Schering Pharma AG)
- Ultra small superparamagnetic iron oxide (USPIO) to detect metastatic disease in lymph nodes (Combidex / Sinerem, Guerbet in EU)
- Superparamagnetic iron oxide associated with dextran for intravenous administration as a MRI contrast medium for the detection of liver lesions that are associated with an alteration in the RES (Endorem/Feridex, Guerbet in EU)

MR-TIP, Magnetic Resonance -Technology Information Portal
NanoCrystal® particles

Characteristics:
- Size below 1 μm
- 100% drug, no carrier
- Generally needed to be stabilized
- Crystalline or amorphous structure
- Increase of dissolution velocity
- Increase in saturation solubility
- Amorphous particle state offers advantage

Claims:
- **Improved bioavailability**, through application of the NanoCrystal® technology brings one or more practical benefits for poorly water soluble compounds:
  - increased rate of absorption
  - reduction in required dose
  - reduction in fed/fasted variability
  - improved dose proportionality
  - smaller dosage forms
  - more convenient dosage forms
  - rapid Formulation Development
  - applicable to all routes of administration any dosage form
- Rapamune, (Sirolimus), Elan/Wyeth
- Emend (Aprepitant), Elan/Merck
- Tricor (Fenofibrate), Elan/Abbot
- Triglide (Fenofibrate), SkyePharma/First Horizon
- Megace ES® (megestrol acetate) Elan/Par Pharm. Co.
## Nanocrystals: technologies

### Technologies:

<table>
<thead>
<tr>
<th>Technology</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precipitation</td>
<td>- finely dispersed drug</td>
<td>- needs to be stabilized</td>
</tr>
<tr>
<td></td>
<td>- good control of desired size</td>
<td>- organic solvent residue</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- not universally applicable, only drugs with certain properties are possible (e.g., soluble in at least one solvent)</td>
</tr>
<tr>
<td>Milling</td>
<td>- low energy technique</td>
<td>- residue from milling media</td>
</tr>
<tr>
<td></td>
<td>- proven by 4 FDA approved drugs</td>
<td>- can be a slow process (several days)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- needs to be stabilized</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- large batches difficult to produce due to size of milling chamber</td>
</tr>
<tr>
<td>Homogenization</td>
<td>- universally applicable</td>
<td>- high energy technique</td>
</tr>
<tr>
<td></td>
<td>- no problem with large batches</td>
<td>- great experience needed</td>
</tr>
<tr>
<td></td>
<td>- fast method (several minutes possibly)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- water free production possible</td>
<td></td>
</tr>
</tbody>
</table>

**High pressure homogenization**

**NanoCrystal®:** Rapamune (clinical data in EPAR)

### Table 6: Incidence of efficacy failure (6 and 12 months; studies 301 and 302)

<table>
<thead>
<tr>
<th></th>
<th>Study 301</th>
<th>Study 302</th>
<th>Study 302</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AZA (n = 161)</td>
<td>SRL 2 mg (n = 284)</td>
<td>SRL 5 mg (n = 274)</td>
</tr>
<tr>
<td>6 months</td>
<td>32.3 (52)</td>
<td>18.7 (53)</td>
<td>16.8 (46)</td>
</tr>
<tr>
<td>p-value</td>
<td>-</td>
<td>0.002</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>12 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 7: Incidence of acute rejection (3, 6 and 12 months; studies 301 and 302)

<table>
<thead>
<tr>
<th></th>
<th>Study 301</th>
<th>Study 302</th>
<th>Study 302</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AZA (n = 161)</td>
<td>SRL 2 mg (n = 284)</td>
<td>SRL 5 mg (n = 274)</td>
</tr>
<tr>
<td>3 months</td>
<td>29.8 (48)</td>
<td>15.1 (43)</td>
<td>8.4 (23)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.0004</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td>29.8 (48)</td>
<td>16.9 (48)</td>
<td>12.0 (33)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.002</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>31.1 (50)</td>
<td>21.8 (62)</td>
<td>14.6 (40)</td>
</tr>
<tr>
<td>p-value</td>
<td>-</td>
<td>0.046</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
NanoCrystal®: Rapamune (clinical in EPAR)

**Graft Survival Rate**

Kaplan-Meier Estimates

*Log Rank Test = 0.052

*SRL+Csa vs SRL
# Nanocrystals: current status

<table>
<thead>
<tr>
<th>TRADENAME</th>
<th>DRUG</th>
<th>INDICATION</th>
<th>TECHNOLOGY</th>
<th>COMPANY</th>
<th>STATUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapamune®</td>
<td>Rapamycin</td>
<td>Immunosuppressive</td>
<td>Nanocrystal® Elan</td>
<td>Wyeth</td>
<td>Marketed</td>
</tr>
<tr>
<td>Emend®</td>
<td>Aprepitant</td>
<td>Anti-emetic</td>
<td>Nanocrystal® Elan</td>
<td>Merck</td>
<td>Marketed</td>
</tr>
<tr>
<td>Tricor®</td>
<td>Fenofibrate</td>
<td>Hypercholesterolemia</td>
<td>Nanocrystal® Elan</td>
<td>Abbott</td>
<td>Marketed</td>
</tr>
<tr>
<td>Megace ES®</td>
<td>Megestrol</td>
<td>Anti-anoretic</td>
<td>Nanocrystal® Elan</td>
<td>Par Pharm.Co.</td>
<td>Marketed</td>
</tr>
<tr>
<td>Triglide®</td>
<td>Fenofibrate</td>
<td>Hypercholesterolemia</td>
<td>IDD-P® Skyepharma</td>
<td>Sciele Pharma Inc.</td>
<td>Marketed</td>
</tr>
<tr>
<td>Semapimod®</td>
<td>Guanylyhydrazone</td>
<td>TNF-α inhibitor</td>
<td>own</td>
<td>Cytokine Pharmasciences</td>
<td>Phase II</td>
</tr>
<tr>
<td>Paxceed®</td>
<td>Paclitaxel</td>
<td>Anti-inflammatory</td>
<td>unknown</td>
<td>Angiotech</td>
<td>Phase III</td>
</tr>
<tr>
<td>Theralux®</td>
<td>Thymectacin</td>
<td>Anti-cancer</td>
<td>Nanocrystal® Elan</td>
<td>Celmed</td>
<td>Phase II</td>
</tr>
<tr>
<td>Nucryst®</td>
<td>Silver</td>
<td>Anti-bacterial</td>
<td>own</td>
<td>Nucryst Pharm.</td>
<td>Phase II</td>
</tr>
</tbody>
</table>
Albumin nanoparticles (Abraxane®)

- Nanoparticle albumin-bound paclitaxel (nab™-paclitaxel; ABI-007; Abraxane®) is a novel CrEL-free formulation of paclitaxel.
- Prepared by high-pressure homogenization of paclitaxel in the presence of serum albumin, resulting in a nanoparticle colloidal suspension.
- Albumin concentration is 3-4%, which is similar to the albumin concentration in the blood.
- Human albumin-stabilized paclitaxel particles have an average size of approximately 130 nm, which allows intravenous infusion without the risk of capillary blockage.
- Nab-paclitaxel can be reconstituted in normal saline at concentrations of 2-10 mg/ml compared with 0.3-1.2 mg/ml for CrEL-paclitaxel; therefore, the volume and infusion time are reduced.
- The nab-paclitaxel formulation provides several practical advantages over CrEL-paclitaxel:
  - premedications for hypersensitivity reactions are not required,
  - the infusion time is shorter (30 min for nab-paclitaxel vs 3 h for CrEL-paclitaxel)
  - and conventional infusion equipment may safely be used since there is no danger of leaching plasticizers from infusion bags or tubing.

Thomas E Stinchcombe
Nanoparticle Albumin-bound Paclitaxel: a Novel Cremophor-EL®-free Formulation of Paclitaxel.
Nanomedicine. 2007;2(4):415-423
Abraxane®

SPARC: Secreted Protein Acidic and Rich in Cysteine

Albumin binds to caveolin-1 receptors and causes the formation of caveolae, to transport albumin across the endothelial membrane.

Transcytosis is the transport of albumin across the endothelial barrier from within the blood vessel to the tumor’s interstitium.

SPARC is then secreted by the tumor to attract and retain albumin-bound nutrients within the tumor cell.

Faculdade de Farmácia da Universidade de Lisboa
iMed.UL (Research Institute for Medicines and Pharmaceutical Sciences)
**Table 10: Mean pharmacokinetic parameters**

<table>
<thead>
<tr>
<th>Dose Abraxane mg/m²</th>
<th>No subjects</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; ng/ml (range)</th>
<th>Vd l/m² (range)</th>
<th>AUC&lt;sub&gt;inf&lt;/sub&gt; ng·hr/ml (range)</th>
<th>T ½ hr (range)</th>
<th>CL t l/hr/m² (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM97-123</td>
<td>200</td>
<td>7757 (6110-10900)</td>
<td>401 (186-656)</td>
<td>8998 (7073-10536)</td>
<td>13.2 (4.6-21.3)</td>
<td>22.9 (19.0-28.4)</td>
</tr>
<tr>
<td></td>
<td>300</td>
<td>13520 (11800-14200)</td>
<td>387 (267-524)</td>
<td>16736 (11530-21749)</td>
<td>14.4 (13.1-18.1)</td>
<td>18.7 (13.8-26)</td>
</tr>
<tr>
<td>CA 005-0</td>
<td>200</td>
<td>13400 (12700-14100)</td>
<td>483 (396-570)</td>
<td>11363 (10042-12683)</td>
<td>18.62 (17.4-19.84)</td>
<td>17.9 (15.8-19.9)</td>
</tr>
<tr>
<td>CA 008-0</td>
<td>260</td>
<td>22969 (4060-86700)</td>
<td>230.7* (53.2-493)*</td>
<td>14789 (5982-28680)</td>
<td>21.6 (16.5-29.6)</td>
<td>21.13 (8.72-43.4)</td>
</tr>
<tr>
<td>CA 012-0</td>
<td>260</td>
<td>18741 (8787-24938)</td>
<td>632 195.5* (348-1831)</td>
<td>17940 (11205-23900)</td>
<td>27.4 (19.8-54.7)</td>
<td>15.2 (10.9-23.2)</td>
</tr>
</tbody>
</table>

*Vdss
Abraxane®: clinical

a) In first-line therapy

b) In second or greater line therapy

P-value = 0.264

P-value = 0.020
Polymeric nanoparticles


Phase I clinical trial and pharmacokinetic evaluation of doxorubicin carried by polyisoheptylcyanoacrylate nanoparticles

Joseph Kattan¹, Jean-Pierre Droz¹, Patrick Couvreur², Jean-Pierre Marino³, Arnaud Boutan-Laroze¹, Philippe Rougier¹, Philippe Brault¹, Henri Vranckx⁴, Jean-Marc Grognet⁵, Xavier Morge⁵, Hélène Sancho-Garnier⁶

¹ Department of Medicine, Institut Gustave-Roussy, Villejuif, France; ² Laboratoire de Pharmacie Galenique et Biopharmacie, URA, CNRS, 1218, Université Paris XI, Chatenay-Malabry, France; ³ Centre de Diagnostic et Prévention Neuro-Vasculaire, Paris, France; ⁴ SOPAR S.A.B. - 1080, Brussels, Belgium; ⁵ Service de Pharmacologie et d’Immunologie, CEA, CE/Saclay, Gif-sur-Yvette, France; ⁶ Department of Statistics and Epidemiology, Institut Gustave-Roussy, Villejuif, France

Keywords: Polymeric nanoparticles, Doxorubicin, drug delivery, cancer therapy.

## Nanoparticles pipeline (overview)

<table>
<thead>
<tr>
<th>Type of carrier and mean diameter (nm)</th>
<th>Drug entrapped or linked</th>
<th>Current stage of development</th>
<th>Type of cancer (for clinical trials)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymer–drug conjugates (6–15)</td>
<td>Doxorubicin, Paclitaxel, Camptothecin, Platinare, TNP-470</td>
<td>12 products under clinical trials (Phases I–III) and in vivo</td>
<td>Various tumours</td>
</tr>
<tr>
<td>Liposomes (both PEG and non-PEG coated) (85–100)</td>
<td>Lurtotecan, platinum compounds, Annamycin</td>
<td>Several products in clinical trials (Phases I–III) and in vivo</td>
<td>Solid tumours, renal cell carcinoma, mesothelioma, ovarian and acute lymphoblastic leukaemia</td>
</tr>
<tr>
<td>Polymeric nanoparticles (50–200)</td>
<td>Doxorubicin, Paclitaxel, platinum-based drugs, Docetaxel</td>
<td>Several products are in clinical trials (Phases I–III) and in vivo</td>
<td>Adenocarcinoma of the oesophagus, metastatic breast cancer and acute lymphoblastic leukemia</td>
</tr>
<tr>
<td>Polymersomes (~100)</td>
<td>Doxorubicin, Paclitaxel</td>
<td>In vivo</td>
<td></td>
</tr>
<tr>
<td>Micelles (lipid based and polymeric) (5–100)</td>
<td>Doxorubicin</td>
<td>Clinical trials (Phase I)</td>
<td>Metastatic or recurrent solid tumours refractory to conventional chemotherapy</td>
</tr>
<tr>
<td>Polymersomes (~100)</td>
<td>Paclitaxel</td>
<td>Clinical trials (Phase I)</td>
<td>Pancreatic, bile duct, gastric and colonic cancers</td>
</tr>
<tr>
<td>Platinum-based drugs (carboplatin/cisplatin), Camptothecin, Tamoxifen, Epirubicin</td>
<td>In vivo and in vitro</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nanoshells (Gold-silica (~130))</td>
<td>No drug (for photothermal therapy)</td>
<td>In vivo</td>
<td></td>
</tr>
<tr>
<td>Gold nanoparticles (10–40)</td>
<td>No drug (for photothermal ablation)</td>
<td>In vivo</td>
<td></td>
</tr>
<tr>
<td>Nanocages (30–40)</td>
<td>No drug</td>
<td>Chemistry, structural analysis and in vitro</td>
<td></td>
</tr>
<tr>
<td>Dendrimers (~5)</td>
<td>Methotrexate</td>
<td>In vitro / in vivo</td>
<td>Metastatic stomach cancer</td>
</tr>
<tr>
<td>Immuno-PGF-liposomes (100)</td>
<td>Doxorubicin</td>
<td>Clinical trials (Phase I)</td>
<td></td>
</tr>
<tr>
<td>Immunoliposomes (100–150)</td>
<td>Doxorubicin, platinum-based drugs, Vinblastin, Vincristin, Topotecan, Paclitaxel</td>
<td>In vivo</td>
<td></td>
</tr>
<tr>
<td>Immunotoxins, Immunopolymers, and fusion proteins (3–15)</td>
<td>Various drugs, toxins</td>
<td>Clinical trials (Phases I–III)</td>
<td>Various types of cancer</td>
</tr>
</tbody>
</table>

**Nanocarriers as an emerging platform for cancer therapy,**
Key factors for design
(in respect of specific medical use)

- Materials Science and Formulation (Technology)
- Understanding underlying basic molecular mechanisms
- Integrating anatomo-physiological issues with pathology or disease state and its progression
- Changes in biological interactions
- Impact in toxicity and efficacy
- Relevance of animal models (In vitro ??! In vivo !!?)
- Differences both in Pharmacokinetics and Pharmacodynamics
- Translational models adapted to specific questions with “nano” (PK/PD versus specific organ toxicity and differential uptake of particles – translocation)
- Important issues in clinical development: How to move faster and safer? Comparability towards specific therapeutic indication?
Specific challenges and opportunities

- **site-specific targeting**
  - Organ
  - Tissue
  - Cell
  - Intracellular

- **cytosolic delivery**
  - Endocytosis molecular mechanisms and how to take advantage for different strategies (siRNA, cytosolic receptor blockade, mitochondrial targeting)
  - Materials purposely designed to overcome intracellular barriers for drug delivery

- **different routes of administration**
  - Parenteral
  - Oral
  - Ocular/Mucosal delivery, Dermal

- **new materials**

Emerging technologies

In vivo nano-imaging of membrane dynamics in metastatic tumor cells using quantum dots.
Specific challenges and opportunities

• combination therapy
  – The trend for reformulation of old APIs, with advantages of combined administration on the same delivery system (issues on quality/stability, PK/PD, clinical, IP, market access)

• potential theranostic approaches
  – Combined system that is able to localize to the target pathophysiology and deliver an appropriate therapeutic agent (both diagnostic and therapeutic functions)

• “follow-on” products
  – A number of unresolved problems will arise if preventive action is not taken on matters related to old products, previously not classified as nanoparticles that are in fact colloidal nanoparticulate systems
Iron oxide similars / Iron nanoparticles

- A number medicinal products containing iron oxide nanoparticles have been approved as “follow on” products (controversial data published in the literature)

Roth et al, Translational Research 2008;151:36-44 (BfArm)

Toblli et al, Arzneimittelforschung 2009;59(4):176–190
Issues

- **Materials Science**
  - Challenges arising from new materials (inorganic nanoparticles, non-biodegradable/non-biocompatible materials, quantum dots, cationic particles and dendrimeric structures, carbon nanotubes)

- **Formulation / Technologies**
  - Adapting existing technologies to new opportunities (e.g. Quality by Design, Process Analytical Technologies)

- **Translational Research**
  - Adequacy of non-clinical methodology before first in man use (relevance of, appropriate toxicity/efficacy biomarkers and barriers related to disease phase and different routes of administration)

- **Clinical development**
  - Comparability: non-inferiority versus superiority (risk-benefit management)

- **Market Access**
  - Comparative pharmacoeconomic assessment
Risk management
(personal view presented previously
during OECD Working Party in Nanotechnology, Vienna September 2009)

- **What are the criteria used to decide that risk management actions are required?**
  - In the medicinal products sector well defined and implemented, not in the medical devices or other borderline areas...

- **How is scientific evidence and uncertainty reflected in subsequent risk management actions?**
  - In the medicinal products area integrated in the product life cycle permanent assessment

- **How are decisions taken? - and how transparent and predictable are they?**
  - Under established regulation framework for medicinal products, with well defined competences and enforcement modalities

- **To what extent is risk management science-based?**
  - Science-driven, based on data on medicinal products compiled with appropriate rules established under globally harmonized (USA, EU, Japan – ICH) guidelines; need care with situation regarding new engineered materials and combination products