New therapeutic strategies based on nanotechnologies: Nanotherapeutics

María José Alonso
The origin of drug delivery nanostructures: nanopharmaceuticals

D.A. La Van, D.M. Lynn and R. Langer
Nature Reviews, 1, 77, 2002
WHY NANOTHERAPEUTICS?
- More efficacious
- Less toxic
- Easier to administer

HOW DO THEY WORK?
- Overcoming barriers
- Targeted controlled delivery
- Preserving stability
- Solubilizing hydrophobic drugs
The biopharmaceutical problems of drugs and vaccines

- Solubility
- Degradability
- Permeability
- Biodistribución
Drug synthesis: Low Mw compounds

Biotecnology: Peptides, proteins DNA, siRNA, …

The majority of drug candidates do not reach Phase I due to solubility/stability problems

More than 40% of active compounds approved in the last decade are biopharmaceuticals: instability and difficulties for overcoming biological barriers
Nanotherapeutics

Therapeutic benefits

Economical benefits

Social benefits

Improved medicines easier to administer

New medicines, nucleic acid-based therapies

More efficacious and less toxic nanomedicines
Some real examples: cancer therapy

<table>
<thead>
<tr>
<th>Active drug</th>
<th>Product name‡</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daunorubicin</td>
<td>DaunoXome</td>
<td>Kaposi’s sarcoma</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Mycet</td>
<td>Combinational therapy of recurrent breast cancer</td>
</tr>
<tr>
<td>Doxorubicin in PEG-liposomes</td>
<td>Doxil/Caelyx</td>
<td>Refractory Kaposi’s sarcoma; ovarian cancer; recurrent breast cancer</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>AmBisome</td>
<td>Fungal infections</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>DepoCyt</td>
<td>Lymphomatous meningitis</td>
</tr>
<tr>
<td>Vincristine</td>
<td>Onco TCS</td>
<td>Non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>Lurtotecan</td>
<td>NX211</td>
<td>Ovarian cancer</td>
</tr>
<tr>
<td>Nystatin</td>
<td>Nyotran</td>
<td>Topical antifungal agent</td>
</tr>
<tr>
<td>All-trans retinoic acid</td>
<td>Altragen</td>
<td>Acute promyelocytic leukaemia; non-Hodgkin’s lymphoma; renal-cell carcinoma; Kaposi’s sarcoma</td>
</tr>
<tr>
<td>Platinum compounds</td>
<td>Platar</td>
<td>Solid tumours</td>
</tr>
<tr>
<td>Annamycin</td>
<td></td>
<td>Doxorubicin-resistant tumours</td>
</tr>
<tr>
<td>*1A gene</td>
<td></td>
<td>Various tumours</td>
</tr>
<tr>
<td>DNA plasmid encoding HLA-B7 and α2 microglobulin</td>
<td>Allovecitin-7</td>
<td>Metastatic melanoma</td>
</tr>
<tr>
<td>Liposomes for various drugs and diagnostic agents (lipoMASC)</td>
<td></td>
<td>Broad applications</td>
</tr>
</tbody>
</table>

*In different countries the same drug could be approved for different indications or be at different phases of clinical trials. ‡Name of liposome formulation.
**DRUG-POLYMER CONJUGATES**

Some real examples: cancer therapy

<table>
<thead>
<tr>
<th>Commercial name</th>
<th>drug</th>
<th>Polymer</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncaspar® (Enzon)</td>
<td>Asparaginasa</td>
<td>PEG</td>
<td>Leucemia</td>
</tr>
<tr>
<td>Zinostatin® (Yamanouchi Pharm)</td>
<td>Neocarzinostatina</td>
<td>Polyestiren-maleic acid</td>
<td>Carcinoma hepatocellular</td>
</tr>
<tr>
<td>Xyotax ®</td>
<td>Paclitaxel</td>
<td>Polyglutamic acid</td>
<td>Fase III (pulmón, ovario)</td>
</tr>
</tbody>
</table>
Some real examples: cancer therapy

**POLYMER NANOPARTICLES AND MICELLES**

<table>
<thead>
<tr>
<th>Commercial name</th>
<th>Composition</th>
<th>Drug</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abraxane ®</td>
<td>Albumin Nanoparticles</td>
<td>Paclitaxel</td>
<td>Mama</td>
</tr>
<tr>
<td>Eloxatin ®</td>
<td>Pglu-PEG Micelles</td>
<td>Cis-platino</td>
<td>Colorectal</td>
</tr>
</tbody>
</table>
Some real examples: cancer therapy

**ABRAXANEx**

- **Mecanism of action:** the nanoparticles leave the blood vessels by a receptor mediated (glycoprotein 60) transcitosis and accumulate in the tumoral tissue due to their interaction with SPARC (protein overexpressed in tumoral cells)

- **No premedication is required to avoid hypersensitivity reactions**

- **Lower infusion time**

**Albumin nanoparticles Containing paclitaxel**

Aproved January 2005 FDA

**Indication:** Metastatic breast cancer
Additional reasons for nanotherapeutics

Future DDS Oncology Market

- Top selling oncology drugs are coming off patent over the next several years
- DDS technology has the potential to extend the life of many drugs for years with formulations better than the original

Pipeline DDS Line Extensions?

- Taxotere (P-IV ANDAs in 2007)
  - ADVENTRX Pharm: lyophilized nano-emulsion formulation of docetaxel
- Arimidex (9 Generics Waiting)
  - Unprotected: zero line extensions in development
- Gemzar (Generics have already filed P-IV ANDAs)
  - Neopharm: liposomal encapsulation (Neolipid)
- Camptosar (Generics have already filed P-IV ANDAs)
  - Meditech: HLA carrier (HyACT)
Biocompatible and biodegradable nanostructures
CURRENT WORK AT THE USC:

Rational design of nanocarriers based upon final applications (resolving problems):

- **Overcoming mucosal barriers:**
  nasal delivery of macromolecules: peptides and vaccines

- **Improving efficacy and reducing toxicity:**
  anticancer drug delivery

- **New nucleic acid based therapies:** pDNA, siRNA
OVERCOMING MUCOSAL BARRIERS: Cyclodextrin/polysaccharide nanocarriers

PROPERTIES:
- Versatile
- Protective effect
- Permeabilizing effect
- Adhesive effect

TECHNOLOGY:
- Mild
- Simple
- Fast
Preparation of CS/CD Nanoparticles:

Ionotropic gelation

Cyclodextrin (CD) + TPP

Chitosan (CS)

Magnetic stirring

CS/CD Nanoparticle suspension

CS/SBE-β-CD nanoparticles
Freeze-dried Chitosan nanoparticles before and after resuspension
OVERCOMING MUCOSAL BARRIERS: Cyclodextrin/polysaccharide nanocarriers

Nasal administration
Chitosan-CD nanoparticles: In vivo Studies in Rabbits

Maximum decrease of blood glucose levels:
- **INSULIN SOLUTION**: <15%
- **CS/CM-β-CD nanoparticles**: 32%
- **CS/SBE-β-CD nanoparticles**: 36%

(n = 6)
OVERCOMING MUCOSAL BARRIERS: Oil/polysaccharide nanocarriers: Nanovaccines

- rHBs Ag
- Chitosan coating
- Oil core – Immunostimulant

Size: 100-400 nm
Ag loading: 90%

22 nm
Oil/polysaccharide nanocarriers: intranasal immunization rHBs Ag

<table>
<thead>
<tr>
<th></th>
<th>Time (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td><strong>Control NE</strong></td>
<td>10µg x 2 i.n.</td>
</tr>
<tr>
<td><strong>NC:Ag 1:12.8</strong></td>
<td>10µg x 2 i.n.</td>
</tr>
<tr>
<td><strong>NC:Ag 1:0.25</strong></td>
<td>10µg x 2 i.n.</td>
</tr>
<tr>
<td><strong>HBsAg-Alum</strong></td>
<td>5µg x 1 i.m.</td>
</tr>
</tbody>
</table>
Oil/polysaccharide nanocarriers: intramuscular immunization rHBs Ag

**Anti-HBsAg IgG (µg/ml)**

- **NC:Ag 1:12.8 - 10µg x 2 i.m.**
- **NC:Ag 1:0.25 - 10µg x 2 i.m.**
- **HBsAg-Alum - 10µg x 2 i.m.**

*NC:Ag 1:0.25 – HBsAg-Alum & NC:Ag 1:12.8*
IMPROVING EFFICACY/REDUCING TOXICITY: anticancer drug delivery

Paul Ehrlich

The Nobel Prize in Physiology or Medicine 1908

"in recognition of their work on immunity"

“The maggie bullet”

“To go straight to the organisms to Which they were aimed”
Poliaminoacid and polysaccharide nanocapsules

Less toxic and more efficacious drugs
NEW NUCLEIC ACID BASED THERAPIES: 
\[\text{pDNA, siRNA}\]

Nanobiopharmaceuticals

“The week link of gene therapy is paradoxically the vehicle rather than the drug itself”

*J.P. Behr, Bioconjugate Chemistry (1994)*
Hyaluronic acid based nanoparticles: Ocular gene therapy

3 días post-instillation

Green channel = Transfected cells: GFP
BIODEGRADABILITY OF HA:CS NANOPARTICLES IN CORNEAL TISSUE

2h post-instilación

flHA

12h post-instilación

flHA:CSO
The future.....

‘Inteligent Therapeutics’

‘Smart Drug Delivery’

- Identification of biomarkers and targets

- New biomaterials: biomimetic/bioinspired
  (molecular recognition, sensitive to biological changes....)

- New techniques for evaluation
Gracias!  María José Alonso: ffmjalon@usc.es

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