NEW LUNG-TUMOUR-PENETRATING NANOCARRIER DESIGNED FOR AEROSOLIZED CHEMOTHERAPY

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• Challenges in lung cancer therapy
  • Current treatment approaches
  • Aerosolized chemotherapy – a new option for treatment?

• Experimental part
  • Design and formulation of an inhalable tumour-targeted nanocarrier
  • *In vitro* and *in vivo* evaluations

• Conclusions and perspectives
CHALLENGES IN LUNG CANCER THERAPY
Lung cancer remains very challenging to treat

- Low drug/nanocarrier concentration in the tumour site
  - Only 0.7% of an injected dose of nanoparticle ends up in a tumour
    - Wilhem et al, Nat Rev Mat 2016

- Systemic toxicities (dose-limiting toxicities)

- Treatment interruption – tumor cell repopulation

- Difficulty for the drug/nanocarrier to distribute throughout solid tumours

- Conventional chemo
- Targeted chemo
- Nanomedicine

Many new identified biomarkers - targets

EGFR, ALK, ROS1, ... Folate receptor?
Aerosolized chemotherapy – a new option for treatment?

- **Clear pharmacokinetic advantage**
  - High drug/nanocarrier doses directly to the lung tumour site
  - Reduction of systemic distribution and toxicities
- **Reduction/suppression of treatment interruption**
- **Access to the lung tumour site through the local bloodstream**
- **Access to the lymphatic system !! Tumour spreading !!**

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- **Poor drug deposition**
- **Logistic and safety challenges**

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- **Pulmonary toxicity**
- **Penetration into the solid tumour**
- **Time of retention within the lung tumour site**

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**Device-related challenges**

**Formulation-related challenges**
EXPERIMENTAL PART
Development of an inhalable tumour-targeting nanocarrier

!! **Folate receptor-α** is overexpressed at the surface of lung cancer cells !!

<table>
<thead>
<tr>
<th>Type of lung cancer</th>
<th>% FR-expressing cancer (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td>66% (511)</td>
</tr>
<tr>
<td><strong>Adenocarcinoma</strong></td>
<td>72% (117)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>51% (71)</td>
</tr>
<tr>
<td>SCLC</td>
<td>25% (24)</td>
</tr>
<tr>
<td>Lung metastases</td>
<td>30% (23)</td>
</tr>
</tbody>
</table>

Paclitaxel-entrapped solid lipid nanoparticles (SLN)

Entrapment efficiency = 99.0 ± 0.3 % (w/w)
Drug loading = 5.1 ± 0.2 % (w/w)

In vitro paclitaxel release profile under physiologic condition

~15% in 24h
Cell binding and uptake of the coated SLN

- Size properties similar to paclitaxel-loaded SLN
- 2 FR-expressing cell lines
  - Human HeLa ovarian adenocarcinoma
  - Mouse M109-HiFR lung carcinoma cell subline
- The SLN seemed to enter FR-expressing cells in vitro

**25-NBD-cholesterol**

F-PEG-HTCC-Alexa Fluor® 405

**PSD of fluorescent SLN**

- Non coated
- Coated

**Human HeLa ovarian adenocarcinoma**

**Mouse M109-HiFR lung carcinoma cell subline**

**Control**

30 min  3 h  6 h
Anti-proliferative properties of the coated SLN MTT assay

Half maximum inhibitory concentration (IC$_{50}$) – 8-hours incubation

- **Cell line-dependent**
- **Multiple pathways involved for the SLN to enter the cells**
- **Involvement of folate receptor-mediated endocytosis**
- **Overcoming the Taxol®-resistance in M109-HiFR?**

**The SLN entered FR-expressing cancer cells**

- Taxol
- Non-coated SLN
- PEG-HTCC-coated SLN
- F-PEG-HTCC-coated SLN
- F-PEG-HTCC-coated SLN + folic acid

HeLa M109-HiFR

- n.s.
- ***
- **
- *
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Two-way ANOVA
Lung tumour distribution of coated SLN after pulmonary delivery

The M109 model

Endotracheal nebulization
Microsprayer™ model 1A-1C
(Penn-Century)

Non-treated M109 mouse

25-NBD-cholesterol
IsolectinB4
F-PEG-HTCC

Treated M109 mouse

25-NBD-cholesterol
IsolectinB4
F-PEG-HTCC

✓ Remarkable penetration into solid lung tumour

Minchinton and Tannock, Nat Rev cancer 2006
CONCLUSIONS AND PERSPECTIVES
Inhalable tumour-targeting nanocarrier

**WO 2015055796 A1**

- Promising results in terms of anti-cancer activity
- Encapsulation and sustained release of paclitaxel
- Able to enter FR-expressing cancer cell lines *in vitro*
- Potentiate the *in vitro* anti-proliferative activity of paclitaxel
- Solid lung tumour-penetrating abilities

**InhaTarget**

Dry powders for inhalation

**Phase I/II**

New animal models
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