Aerosol therapy of mAbs
administration by aerosol

Nathalie Heuzé-Vourc’h

Financial supports:
Aerosol therapy
Aerosol therapy for drugs with systemic action

- Airways as a portal for systemic effects

Air-blood barrier = 75 m²

Small molecules: fentanyl, apomorphine hydrochloride

Biologics: insulin (Afrezza®, MannKind Corporation)
Aerosol therapy of drugs with local action
Respiratory diseases

small molecules: b2-adrenoreceptor agonists, muscarinic antagonists and corticosteroids

biologics: Dornase alfa (Pulmozyme®, Roche)
Aerosol therapy of Antibody-based therapeutics in respiratory diseases

- Approved or in Phase III clinical studies

<table>
<thead>
<tr>
<th>Sponsoring company</th>
<th>INN or code name</th>
<th>Molecular format</th>
<th>Target(s)</th>
<th>Current Phase</th>
<th>Phase III indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genentech/Roche - Novartis</td>
<td>Omalizumab</td>
<td>Humanized IgG1</td>
<td>IgE</td>
<td>Approved</td>
<td>Asthma</td>
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<tr>
<td>MedImmune</td>
<td>Palivizumab</td>
<td>Humanized IgG1</td>
<td>RSV</td>
<td>Approved</td>
<td>Prevention of RSV infection</td>
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<tr>
<td>Genentech/Roche</td>
<td>Bevacizumab</td>
<td>Humanized IgG1</td>
<td>VEGF</td>
<td>Approved</td>
<td>NSCLC</td>
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<tr>
<td>GlaxoSmithKline</td>
<td>Mepolizumab</td>
<td>Humanized IgG1</td>
<td>IL-5</td>
<td>Phase III</td>
<td>Asthma; hypereosinophilic syndrome; chronic obstructive pulmonary disease with eosinophilic bronchitis</td>
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<tr>
<td>Teva</td>
<td>Reslizumab</td>
<td>Humanized IgG4</td>
<td>IL-5</td>
<td>Phase III</td>
<td>Eosinophilic asthma</td>
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<tr>
<td>AstraZeneca</td>
<td>Benralizumab</td>
<td>Humanized IgG1</td>
<td>IL-5R</td>
<td>Phase III</td>
<td>Asthma</td>
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<tr>
<td>Hoffmann-La Roche</td>
<td>Lebrikizumab</td>
<td>Humanized IgG4</td>
<td>IL-13</td>
<td>Phase III</td>
<td>Severe asthma</td>
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<td>Peregrine</td>
<td>Bavituiximab</td>
<td>Chimeric IgG1</td>
<td>Phosphatidylserine</td>
<td>Phase III</td>
<td>NSCLC</td>
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<tr>
<td>Genentech/Roche</td>
<td>MPDL3280A</td>
<td>Human IgG1; Fc engineered</td>
<td>Programmed death-ligand 1</td>
<td>Phase III</td>
<td>NSCLC</td>
</tr>
</tbody>
</table>

Inhalation ? ALX-0171 (Ablynx, anti-RSV nanobody™)

Respard et al. 2015
Rationale to deliver antibody-based therapeutics through the airways


i.v. s.c. (adalimumab, omalizumab)

i.m. (palivizumab)

150 KDa protein

500-10,000 less than in the bloodstream

= target site

is mAb delivery through the airways feasible and relevant for respiratory disease treatment?
Therapeutic efficacy of mAbs delivered through the airways

A549 Luc – human NSCLC

**Strength**
- one lesion, alveolar diffusion
- bioluminescence imaging

**Weakness**
- immunodeficient animal
- do not cross-react with murine EGFR

Kras LA1 model

**Strength**
- lepidic NSCLC (natural history)
- normal immune system

**Weakness**
- multiple foci
Cetuximab, anti-EGFR in A549-Luc nude mice

Fate of inhaled monoclonal antibodies after the deposition of aerosolized particles in the respiratory system. Guilleminault L et al. J Control Release. 2014
anti-VEGF in Kras LA1 mice

VEGF neutralizing aerosol therapy in primary pulmonary adenocarcinoma with K-ras activating-mutations. Hervé V et al. MAbs. 2014
**anti-VEGF in Kras LA1 mice**

VEGF IHC in Kras LA1 model during tumorigenesis

*VEGF neutralizing aerosol therapy in primary pulmonary adenocarcinoma with K-ras activating-mutations. Hervé V et al. MAbs. 2014*
Anti-VEGF in Kras LA1 model
anti-VEGF limited tumor angiogenesis

Inhibition of VEGFR2 pathway:

Microvascular density:

<table>
<thead>
<tr>
<th></th>
<th>Control 10 mg/kg</th>
<th>G6-31 10 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small vessel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VWF % (± SEM)</td>
<td>+ 9.85 (± 20.05)</td>
<td>- 44.21 (± 7.67)</td>
</tr>
<tr>
<td>p</td>
<td>0.96</td>
<td>0.018</td>
</tr>
<tr>
<td>Large vessel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VWF % (± SEM)</td>
<td>- 43.10 (± 12.09)</td>
<td>- 11.50 (± 14.69)</td>
</tr>
<tr>
<td>p</td>
<td>0.0096</td>
<td>0.27</td>
</tr>
</tbody>
</table>

VEGF neutralizing aerosol therapy in primary pulmonary adenocarcinoma with K-ras activating-mutations. Hervé V et al. MAbs. 2014
Anti-VEGF in Kras LA1 model anti-VEGF limited tumor growth

Proliferative index:

VEGF neutralizing aerosol therapy in primary pulmonary adenocarcinoma with K-ras activating-mutations. Hervé V et al. MAbs. 2014
Biodistribution of mAbs delivered through the airways

A549 Luc – human NSCLC

NIRF imaging
✓ cetuximab conjugated to a fluorophore

IHC for cellular localization
✓ anti-human IgG

cetuximab anti-EGFR (human) (Merck)
Biodistribution of mAbs delivered through the airways

Fate of inhaled monoclonal antibodies after the deposition of aerosolized particles in the respiratory system. Guilleminault L et al. J Control Release. 2014
Biodistribution of mAbs delivered through the airways

Fate of inhaled monoclonal antibodies after the deposition of aerosolized particles in the respiratory system. Guilleminault L et al. J Control Release. 2014
Pharmacokinetics of mAbs delivered through the airways

mAbs (only full-length)
✓ anti-VEGF (G6-31, Genentech)
✓ Anti-EGFR (cetuximab, Merck)
✓ Anti-CD20 ....

Animals
✓ WT animals
Healthy/tumor model

mAbs (only full-length)
✓ Anti-EGFR (cetuximab, Merck)
✓ Anti-ricin (43RCA, French Army)

Devices
✓ Microsprayer™ (PennCentury)
✓ Mesh nebulizer (Aerogen)
Pharmacokinetics of mAbs delivered through the airways

Serum bioavailability (F)

- G6-31 (Kras LA1 mice) 5.1%
- cetuximab (normal mice) 3.9%
- rituximab (normal mice) 6.2%
- cetuximab (NHP) 0.3%
- Anti-ricin (NHP) <1%

Mean residence time (MRT)

- cetuximab (normal mice) 12.4 days
- rituximab (normal mice) 14.2 days
- cetuximab (NHP) 10.9 days

Fate of inhaled monoclonal antibodies after the deposition of aerosolized particles in the respiratory system. Guilleminault L et al. J Control Release. 2014
Pharmacokinetics of mAbs delivered through the airways

- Role of FcRn in the passage from the airways into the bloodstream

**BL6 WT**

**Blood sampling**

cetuximab or rituximab
one administration, 10mg/kg
i.v. or aerosol

**Blood sampling**

**PK analysis**

**BL6 KO FcRn**

**PK analysis**

Fate of inhaled monoclonal antibodies after the deposition of aerosolized particles in the respiratory system. Guilleminault L et al. J Control Release. 2014
Pharmacokinetics of mAbs delivered through the airways

**Table 2**
Estimated non-compartmental pharmacokinetic parameters for cetuximab in WT and FcRn KO mice. AUC: area under the concentration–time curve; AUMC: area under the first-moment concentration–time curve; MRT: mean residence time; $t_{1/2}$: half-life for elimination; MAT: mean absorption time; F: bioavailable fraction.

<table>
<thead>
<tr>
<th>CETUXIMAB</th>
<th>FcRn WT</th>
<th>FcRn KO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I.v. route</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$AUC_{0\rightarrow \infty}$ ($\text{mg}\cdot\text{L}^{-1}\cdot\text{day}$)</td>
<td>942.9</td>
<td>39.0</td>
</tr>
<tr>
<td>$AUMC_{0\rightarrow \infty}$ ($\text{mg}\cdot\text{L}^{-1}\cdot\text{day}^2$)</td>
<td>9851.4</td>
<td>19.4</td>
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<tr>
<td>MRT (day)</td>
<td>10.4</td>
<td>0.5</td>
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<tr>
<td>$t_{1/2}$ (day)</td>
<td>7.2</td>
<td>0.3</td>
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<tr>
<td><strong>Pulmonary route</strong></td>
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<td></td>
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<tr>
<td>$AUC_{0\rightarrow \infty}$ ($\text{mg}\cdot\text{L}^{-1}\cdot\text{day}$)</td>
<td>37.0</td>
<td>3.1</td>
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<tr>
<td>$AUMC_{0\rightarrow \infty}$ ($\text{mg}\cdot\text{L}^{-1}\cdot\text{day}^2$)</td>
<td>456.8</td>
<td>3.8</td>
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<tr>
<td>MRT (day)</td>
<td>12.4</td>
<td>1.2</td>
</tr>
<tr>
<td>$t_{1/2}$ (day)</td>
<td>8.6</td>
<td>0.9</td>
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<tr>
<td><strong>F</strong></td>
<td>3.9%</td>
<td>7.9%</td>
</tr>
<tr>
<td><strong>MAT</strong> (day)</td>
<td>1.9</td>
<td>0.7</td>
</tr>
</tbody>
</table>

*Fate of inhaled monoclonal antibodies after the deposition of aerosolized particles in the respiratory system. Guilleminault L et al. J Control Release. 2014*
Conclusions

✔ mAb delivery through the airways is “therapeutically” relevant

- Reach their target antigen and pharmacologically effective
- Limited passage into the bloodstream

_in pathophysiological conditions_?

_not only dependent on FcRn – lymph vessels_?

- Safety/immunogenicty
Issues related to Aerosol therapy

Drug

Device and Aerosol

Respiratory parameters of the patient
Issues related to Aerosol therapy

- Complexed macromolecules (150 KDa)
- Prone to chemical/physical degradation (in particular at the air-liquid interface)
Issues related to Aerosol therapy

Renaud Respaud
Aerosol formulations

Laurent Vecellio
Nebulisation devices

Renaud Respaud
Aerosol formulations

Laurent Vecellio
Nebulisation devices

DEVICE and AEROSOL

DRUG

RESPIRATORY PARAMETERS
OF THE PATIENT