Shedding of viral vectors during clinical gene therapy

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Literature study on shedding data viral vectors

Spin-off of project carried out for Dutch Commission on Genetic Modification to advise on standardisation of shedding assays

**Design literature study**

- PubMed search of published trials till 31 July 2006
- Retroviral, Ad, AAV, poxviral (vaccinia & canarypox) vectors
- Shedding = dissemination of vector in any form into the environment through excreta from treated subject
- Excreta = urine, faeces, sweat, saliva, nasopharyngeal fluids, skin, semen (+ blood for local administration)
- Occurrence of RCR and RCA
## Results literature search

<table>
<thead>
<tr>
<th>Vector</th>
<th>Total</th>
<th>With shedding data</th>
<th>Patient no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retroviral</td>
<td>73</td>
<td>27 (37%)</td>
<td>445</td>
</tr>
<tr>
<td>Adenoviral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>replication-deficient</em></td>
<td>106</td>
<td>50 (47%)</td>
<td>869</td>
</tr>
<tr>
<td><em>crad</em></td>
<td>25</td>
<td>11 (44%)</td>
<td>173</td>
</tr>
<tr>
<td>AAV</td>
<td>9</td>
<td>7 (78%)</td>
<td>84</td>
</tr>
<tr>
<td>Poxviral</td>
<td>47</td>
<td>5 (11%)</td>
<td>48</td>
</tr>
<tr>
<td><strong>All vectors</strong></td>
<td>260</td>
<td>100 (38%)</td>
<td>1619</td>
</tr>
</tbody>
</table>
Shedding analysis characteristics and shedding data

See our recent publication:

E.A.M. Schenk-Braat et al.
An inventory of shedding data from clinical gene therapy trials.
Conclusions

- Shedding of viral vectors occurs in the clinical practice, no indication for RCA and RCR

- Majority of publications do not report on shedding analysis (data available but not included or shedding analysis not required by national regulatory authorities?)

- Shedding depends mainly on type of vector and way of administration

- Limited data on testing environment may suggest no contamination of hospital environment (however, not representative for “real world” due to hospital safety measures)
Shedding occurs, but ....

- Shedding analysis mainly performed by PCR in non-quantitative way, limited data on infectious particles

- Lack of information on assay characteristics like sensitivity

- No uniformity in shedding analysis → data hard to compare

- Hardly any data on analysis of environment and third persons

- Impact of exposure to vector unknown, will depend on replication capability and type of transgene

- Critical level of shedding to induce infection of third persons unknown
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Shedding data: a snapshot

Retroviral vectors (27 publications)

- Shedding in 11 out of 16 in vivo studies
  - vector in blood after intratumoral administration
  - within first 28 days after therapy
- No RCR in 445 tested patients

Replication-deficient adenoviral vectors (50 publications)

- Shedding in 29 out of 50 studies
  - type of excreta depending on way of administration
  - in general shortlasting
- Semen tested in 2 studies (1 and 12 patients)
  - 1 patient positive 14 days after intraprostatic administration
- No RCA in 201 tested patients
- 4 studies: no vector or RCA in health care personnel
Shedding data: a snapshot

CRAd vectors (11 publications)
- Shedding in blood after administration (8 out of 11 studies)
  - during few hours to 76 days
- 1 study: shedding of infectious particles in urine up to 8 days after intraprostatic administration

AAV vectors (7 publications)
- Shedding in nasopharyngeal samples (4 out of 5 CF studies)
- Shedding in 2 studies on hemophilia B:
  - intramuscular: saliva & serum +, semen & urine -
  - intraarterial: semen & urine +

Pox viral vectors (5 publications)
- Shedding in wound scab (1 out of 5 studies)
- 1 study: live virus only found in wound dressing