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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

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Results literature search

Vector	Number of publications		Patient no.
	Total	With shedding data	
Retroviral	73	27 (37%)	445
Adenoviral			869
replication-deficient	106	50 (47%)	
crad	25	11 (44%)	173
AAV	9	7 (78%)	84
Poxviral	47	5 (11%)	48
All vectors	260	100 (38%)	1619

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.

J Gene Med 2007;9:910-921.

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)

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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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Literature study published in J Gene Med 2007;9:910-921.

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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

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Shedding data: a snapshot

CRAd vectors (11 publications)

- Shedding in blood after it 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

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