

New trends in the Netherlands

The background is a dark blue gradient that transitions to a lighter blue at the bottom. A thin, light blue curved line starts from the left edge and curves downwards towards the center. A larger, light blue shape, resembling a stylized 'N' or a curved arrow, is positioned in the lower right quadrant, pointing towards the bottom right corner.

New trends in the Netherlands

New trends *and* the Netherlands

(correction)

New trends in the Netherlands

New trends in the Netherlands
and worldwide

(addition)

Gene therapy:
lessons from the past &
prospects for the future

with a focus on the Dutch situation

OUTLINE PRESENTATION

Background (COGEM) report

Presentation report (selected topics)

Vectors

Clinical studies

Future trends

*Note: presentation does not
necessarily represent opinion of the
COGEM*

Aim & topic report

Overview of the state of the art of gene therapy and trends for the future in order to anticipate on factors that are relevant for the assessment of risks for man and environment.

Methods

- Literature study
- Analysis of (international) reports
- Interviews with (Dutch) experts
- Attending relevant presentations

Interviews

- Prof. C. Bangma
clinician EUR
- Dr. J. Boesen
CEO AMT
- Dr. E. Braakman
immunologist EUR
- Prof.dr. H.J. Haisma
president NVGT
- Dr. M. Havenga
v-p research Crucell
- Prof.dr. J. Verhaagen
neurobiologist NIH
- Dr. A.R. Wafelman
pharmacist LUMC
- Dr. G. Wagemaker
researcher EUR

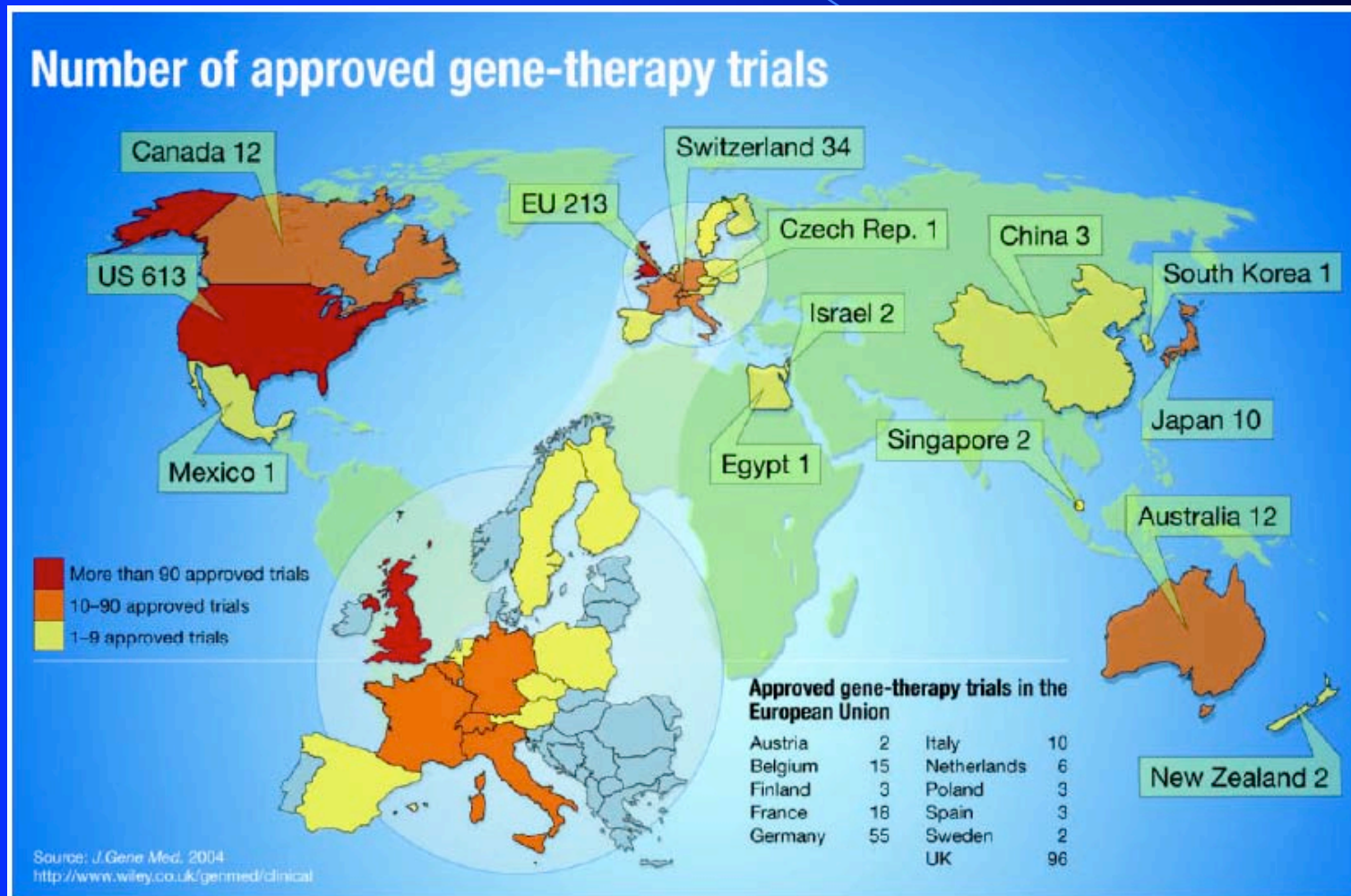
Relative use vectors in clinical gene therapy protocols

vector	1995	2004
Retroviruses	72%	28%
Adenoviruses	14%	26%
Lipofection	11%	9%
Naked/plasmid DNA	2%	14%
Other DNA viral vectors	1%	14%
Other RNA viral vectors		1%
Other vectors		3%
N/C		5%

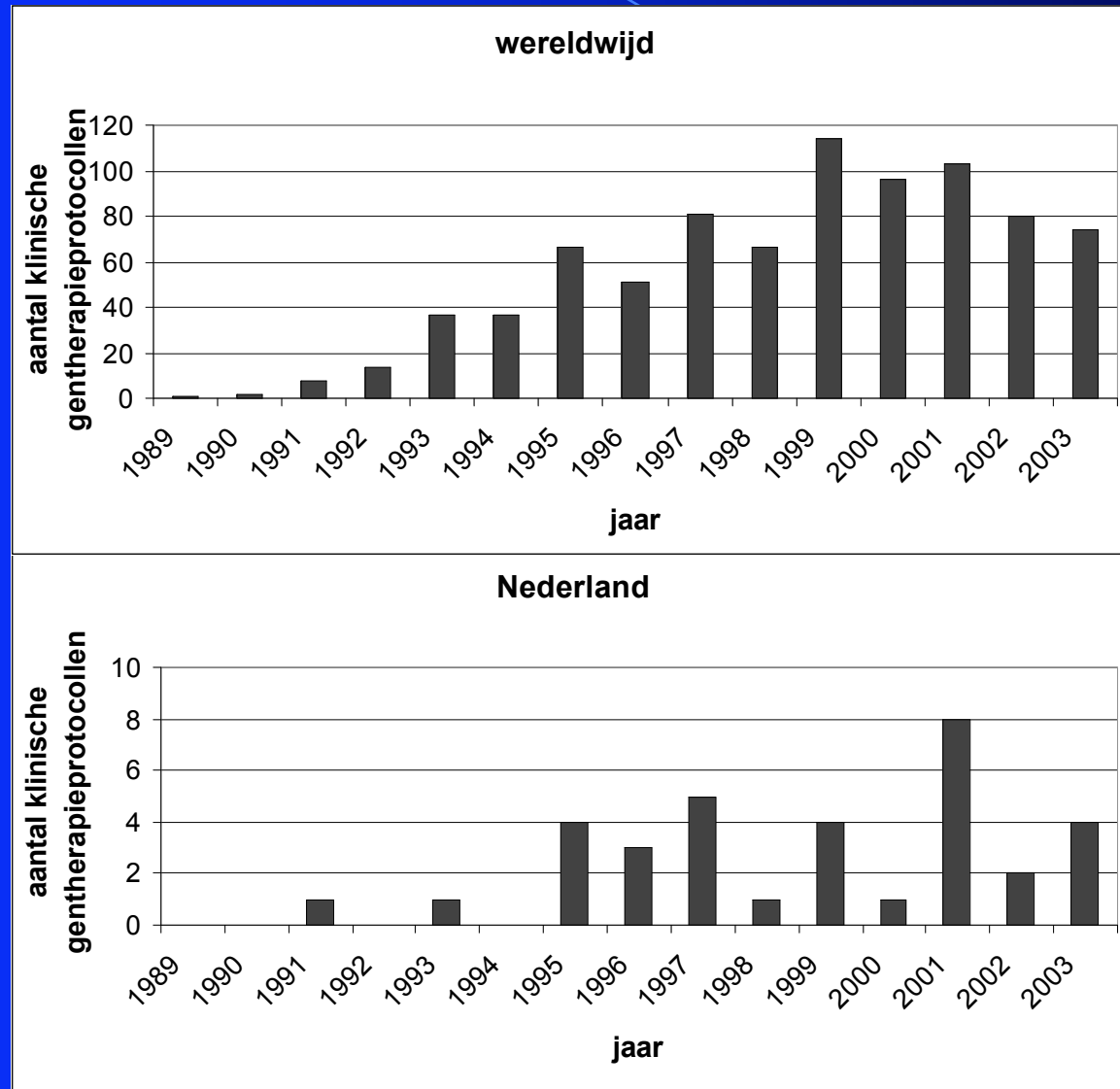
Indications for clinical gene therapy trials

indication	1995	2004
Cancer	49%	66%
Gene marking	24%	6%
Monogeneic diseases	19%	10%
Infectious diseases	8%	7%
Vascular diseases		8%
Other diseases		3%
Healthy volunteers		1%

Approved clinical protocols (I)



Approved clinical protocols (II)



Clinical gene therapy protocol

Besluit GGO

Besluit BCB

Besluit BIF

GT protocol

Min VROM

^ Bureau GGO

^ *COGEM*

Go / no go

CCMO

Go / no go

Inspectie voor
Volksgezondheid

^ *RIVM*

Go / no go

Results clinical studies

- Majority of studies phase I
- > 5000 patients treated so far
- Mild side effects (mostly fever)
- Two incidents
 - death Jesse Gelsinger
(very high dose Ad)
 - 2 X-SCID patients with leukemia
(RV insertional mutagenesis)

Results clinical studies

Positive results:

- Hemophilia (AAV - Factor IX)
- Critical limb ischaemia (Ad VEGF, naked DNA VEGF)
- X-linked SCID (RV _ IL2RG)

Trends

- (Genetic) modification of viral vector tropism
 [*increase specificity*]
- Selective replication of viral vectors
 [*increase dosage locally*]
- Evasion of the immune system
 [*increase persistence vector*]
- Combination therapy
 [*increase effectivity*]

Relevant issues for risk assessment

- Shedding
- Germline transmission
- Insertional mutagenesis
- Transgene

Support for risk assessment

- Generation of new data
[*further development of animal models*]
- Accessibility of existing data
[*standardization eg. vectors / clinical protocols*
databanking eg. results clinical studies / insertion sites]

Gene therapy in the Netherlands

- Time to acceptance clinical gene therapy protocol [Loket Gentherapie]
- Financing [ZonMW]
- Accessibility clinical gene therapy studies
 - > overview studies / responsible investigator / number of patients enrolled / still open
 - > English version

Acknowledgements

Virus Biology lab (prof. R.C. Hoeben)
Dept of Molecular Cell Biology
Leiden University Medical Centre



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Erasmus MC, dept Hematology

EU project: Concerted Safety and Efficiency Evaluation of Retroviral Transgenesis for Gene Therapy of Inherited Diseases