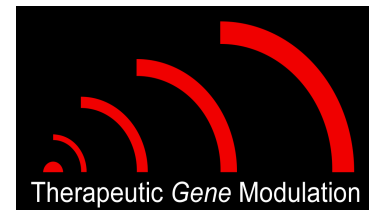


# *De ontwikkeling en toekomst van gentherapie in Nederland*

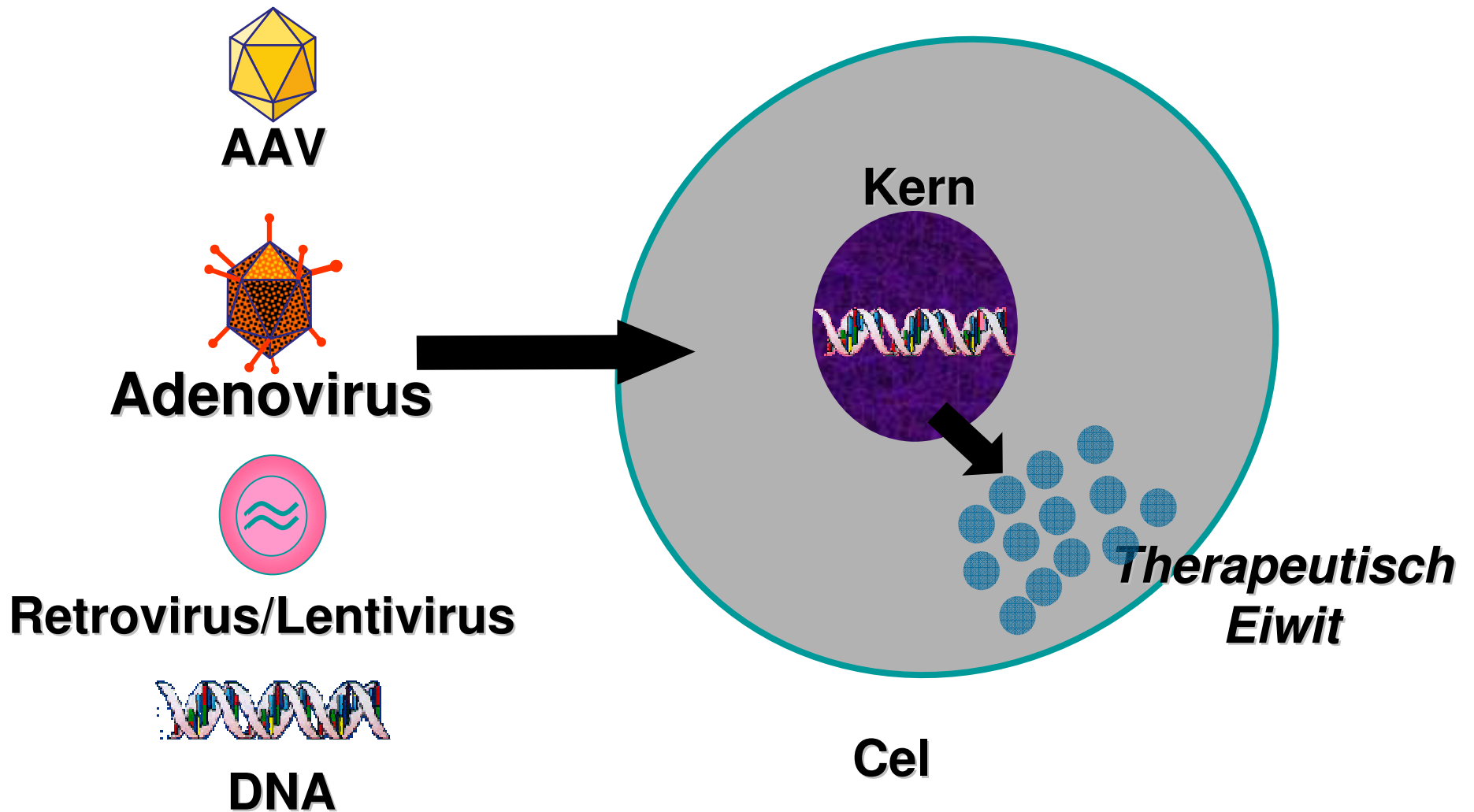
Forum Biotechnologie & Genetica  
10 april 2008

Prof. Dr. Hidde J. Haisma  
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Rijksuniversiteit Groningen

[www.farm.rug.nl/tgm](http://www.farm.rug.nl/tgm)



# Gentherapie Principe



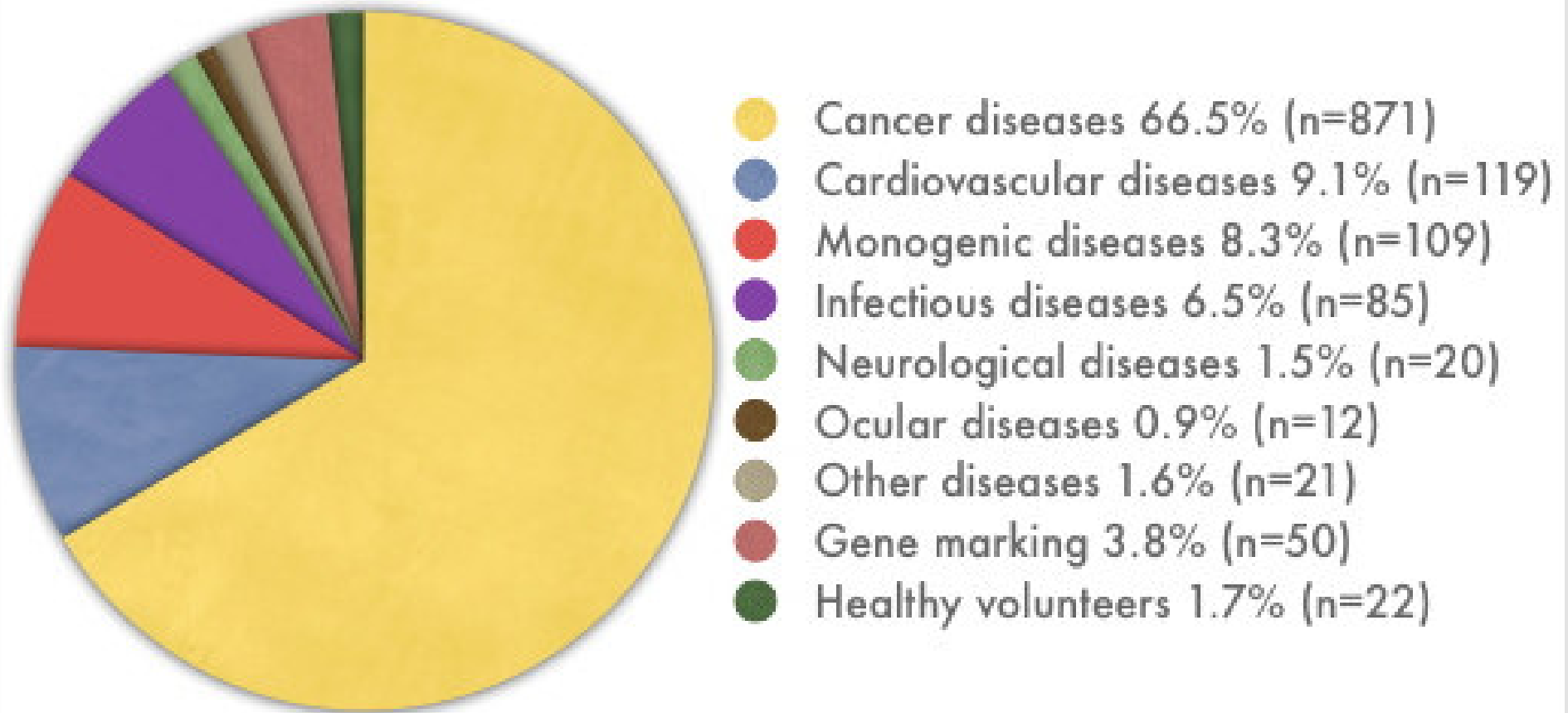
# Gentherapie benaderingen

- **Mutatie compensatie:**
  - Monogenetische ziekten
- **Cel als geneesmiddelfabriek:**
  - factor VIII, hemofilie
- **Suicide gentherapie:**
  - kanker

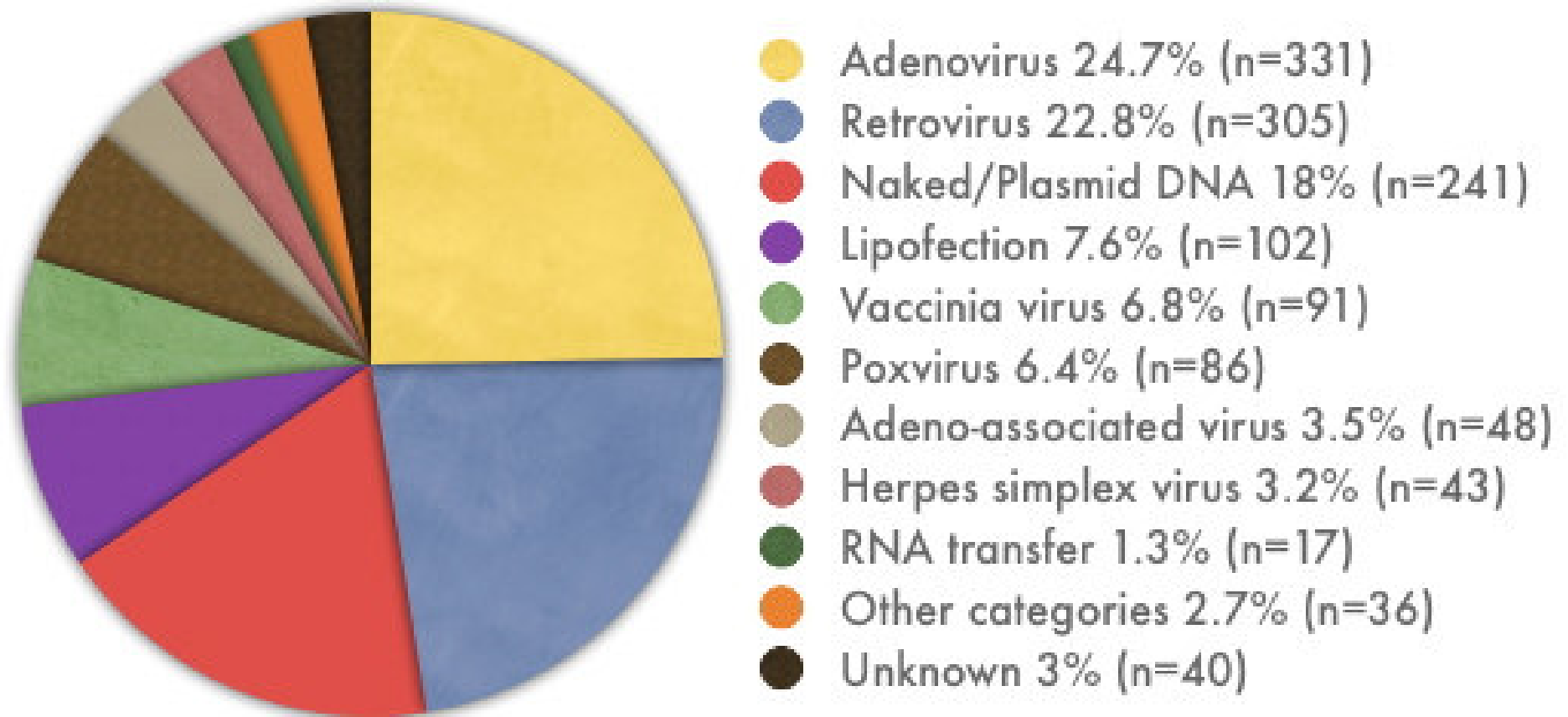
# Gentherapie

- **Successen:** kanker, cardiovasculair, hemofilie, rheuma, immuundeficientie, vaccins
- **Risico's:** dosering, mutaties, toxiciteit
- **Ontwikkeling:** selectiviteit, tijdsduur, regulatie  
locaal versus systemisch

## Indications Addressed by Gene Therapy Clinical Trials



## Vectors Used in Gene Therapy Clinical Trials



## Therapy on trial

The death of a participant in a gene therapy trial has thrown the entire field into question—as it did once before in 1999. Can the field survive this second setback? Virginia Hughes investigates.

nature  
biotechnology

## Gene editing in human stem cells using zinc finger nucleases and integrase-defective lentiviral vector delivery

Advance Online Publication | doi:10.1038/nature450485a | Published online 14 November 2007

nature

## NEWS & VIEWS

## Companies jostle for lead in RNAi, despite uncertainties

Commercial activity in the RNA interference (RNAi) space continues apace, even with key challenges related to interpretation of the technology, a wall of regulatory issues and several intellectual property (IP) contests remaining.

In early September, Alnylam Pharmaceuticals, of Cambridge, Massachusetts, teamed with Isis Pharmaceuticals, of Carlsbad, California, in a joint venture called Regulus Therapeutics in Carlsbad, California, which will explore microRNA (miRNA), touted as likely to yield the next generation of RNA therapeutics. About a dozen days later, Alnylam entered ties with

the therapeutic areas in which Merck does research” and did not believe it would be able to do so “within the confines” of its Alnylam deal. As such, the companies went their separate ways.

Although pharma’s whopper bets on RNAi drugs continue—London-based AstraZeneca signed a potential £200 (\$407) million licensing agreement this year with Silence Therapeutics, of London, for respiratory-disease targets—successful commercialization faces several challenges, the key hurdle being delivery. It’s possible to get the drug into some solid tumors and organs such as the liver and the eyes, but safety and selectivity “are two major challenges that still need

http://www.nature.com/naturebiotechnology

### STEM CELLS

## Primates join the club

Ian Wilmut and Jane Taylor

Researchers have achieved the testing goal of generating embryonic stem cells from a primate. The procedure used could provide insights into a variety of diseases, if

http://www.nature.com/naturebiotechnology

## Positive clinical data in Parkinson’s and ischemia buoy gene therapy

The rehabilitation of gene therapy is gaining momentum, as positive news on both the clinical and commercial fronts suggests the field is closer than ever to a long-awaited success, particularly for disorders that represent niche, unmet medical needs. With a steady accumulation of positive data in multiple indications, not only are investors and biotech firms showing renewed interest, but also large pharmaceutical companies are back in the game. But with many false dawns before, researchers remain cautious about timelines for approval.

Asked whether a gene therapy could be registered within the year, Inder Verma, gene therapy pioneer and professor in the Laboratory of Genetics at the Salk Institute of Biological Studies, in La Jolla, California, cautions, “I just don’t think there’s enough phase 3 data out to say that.” Verma thinks an approval in “2010 is more realistic, at least for cancer vaccines.”



See related article, pages 1626–1633

### Cell-Based GATA4 Cardiac Gene Transfer Using Cell-Penetrating Peptide

Tong Tang, H. Kirk Hammond

## NEWS

### ALSO IN THIS SECTION

Clinical setbacks for toll-like receptor9 agonists in cancer p825

Uncertainty surrounds cancer vaccine review at FDA p827

Ann Arbor community rallies in wake of Pfizer shutdown p829

News in brief p831

Table 2. Completed clinical gene therapy trials in The Netherlands

Clinical centre (protocol ID)	Medical condition	Trial concept	Number of patients
<i>1. Correction of a genetic defect</i>			
LUMC (IM 91-008/93-008)	SCID	Correction of ADA deficiency by transplantation of autologous bone marrow cells transduced with retroviral vector encoding ADA gene [19]	3
<i>2. Suicide gene therapy for cancer</i>			
EMC (IM 98-007)	Malignant glioma	Killing tumor cells by intratumoral administration of adenoviral vector encoding herpes simplex thymidine kinase gene followed by ganciclovir treatment [50]	14
EMC (IM 99-015)	Prostate cancer	Killing tumor cells prior to surgery by intratumoral administration of adenoviral vector encoding herpes simplex thymidine kinase gene followed by GCV treatment [46]	12
UMCG & LUMC (IM 95-004/95-015 <sup>4</sup> )	Glioblastoma multiforme	Killing tumor cells by intratumoral administration of cells producing retroviral vector encoding herpes simplex thymidine kinase gene followed by GCV treatment [48,51]	48 + 248 <sup>4</sup>
VUmc (IM 01-001)	Liver cancer	Killing tumor cells by intratumoral administration of adenoviral vector encoding nitroreductase gene (CTL102) followed by treatment with CB1954 [52]	3 (out of 18 in a multicentre trial)
<i>3. Immuno-gene therapy for cancer</i>			
LUMC (IM 01-009)	Metastasized melanoma	Induction anti-tumor immune response by subcutaneous vaccination with allogeneic melanoma cell line transduced with plasmid encoding interleukin-2 gene [45]	33
LUMC (not available)	Metastasized colorectal cancer	Induction anti-tumor immune response by intravenous administration of canarypox viral vector encoding p53 gene [53]	16
LUMC (IM 99-018/01-005)	Melanoma	Induction anti-tumor immune response by intradermal and intracutaneous vaccination with canarypox viral vector encoding miniMAGE-1/3 [54]	1 (out of 40 in a multicentre trial)
NKI (not available)	Metastasized melanoma	Induction anti-tumor immune response by intra- and subcutaneous vaccination with autologous tumor cells transduced with retroviral vector encoding GM-CSF gene [55]	28
UMCG (IM 95-010)	Superficial solid tumors	Induction anti-tumor immune response by intratumoral administration of canarypox viral vector encoding IL-2 gene [56]	3 (out of 15 in a multicentre trial)
UMCG (IM 96-007)	Superficial solid tumors	Killing tumor cells by intratumoral administration of adenoviral vector encoding p53 gene [57]	2 (out of 6 in a multicentre trial)
<i>4. Other gene therapy applications</i>			
AMC (not available)	Crohn's disease	Modulation inflammation by oral administration of transgenic <i>Lactococcus lactis</i> bacteria expressing IL-10 gene [58]	10
UMCG (IM 99-010 <sup>44</sup> )	End-stage coronary artery disease	Enhancement vascularization by intramyocardial administration of naked DNA encoding VEGF2 gene [59]	10
UMCG & LUMC (IM 99-012 <sup>444</sup> )	Critical limb ischaemia in	Enhancement vascularization by intramuscular administration of naked DNA encoding VEGF2 gene [49]	54

Table 3. Ongoing clinical gene therapy trials in The Netherlands

Clinical centre (protocol ID)	Medical condition	Trial concept	Number of patients
<i>1. Correction of a genetic defect</i>			
AMC (IM 05-001 <sup>*,#</sup> )	Genetic lipoprotein lipase deficiency	Correction LPL deficiency by intramuscular administration of AMT-010, an AAV vector encoding lipoprotein lipase variant S447X (LPL S447X)	Inclusion of 8 out of 50 patients completed
LUMC (not available <sup>*,#</sup> )	Duchenne muscular dystrophy	Restoration dystrophin production by intramuscular administration of antisense oligoribonucleotide (exon skipping)	Inclusion of 4 patients completed
<i>2. Suicide gene therapy for cancer and other diseases</i>			
LUMC (IM 03-001)	Loosened hip protheses	Killing interface tissue around implant by intraarticular administration of adenoviral vector encoding nitroreductase gene followed by treatment with CB1954	Inclusion of 12 patients completed
UMCU (IM 97-020 <sup>#</sup> )	Hematological malignancies	Modulation GvHD and GvL disease after allogeneic stem cell transplantation by transplantation of allogeneic donor T lymphocytes transduced with retroviral vector encoding herpes simplex thymidine kinase gene followed by timed GCV treatment	No patients included yet (10 patients projected)
<i>3. Immuno-gene therapy for cancer</i>			
EMC (IM 97-014)	Metastasized renal cell carcinoma	Killing tumor cells by transplantation of autologous T lymphocytes retargeted against carbonic anhydrase IX using a retroviral vector	Inclusion of 5 out of 30 patients completed <sup>*,#</sup>
VUmc (IM 03-008)	Metastasized prostate cancer	Induction anti-tumor immune response by vaccination with two prostate cancer cell lines transduced with AAV vector encoding GM-CSF gene (CG1940 and CG8711) in combination with MDX-010 immunotherapy	Inclusion of 12 out of 41 patients completed

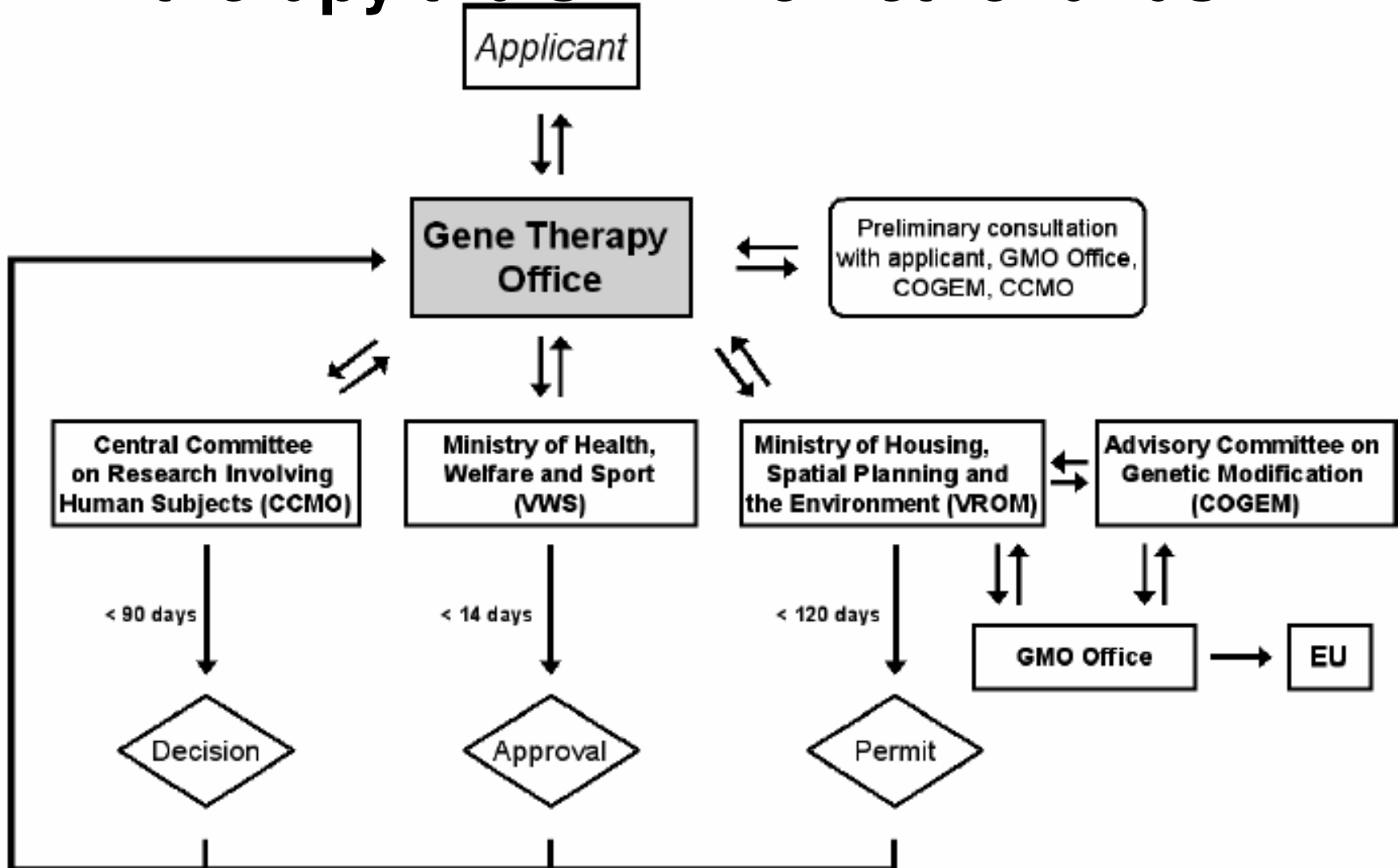
Table 4. Future clinical gene therapy trials in The Netherlands

Clinical centre (protocol ID)	Medical condition	Trial concept
<i>1. Correction of a genetic defect</i>		
AMC (not available yet <sup>#</sup> )	Crigler-Najjar syndrome	Correction of deficiency of the hepatic enzyme UGT1A1 using an AAV vector
EMC (not available yet <sup>#</sup> )	XLA and SCID	Correction of genetic defect in autologous stem cells using a retroviral vector
IOI (not available yet <sup>#</sup> )	Leber congenital amaurose	Correction of CRB1 gene expression in the retina using an AAV vector
<i>2. Suicide gene therapy for cancer</i>		
AZM (IM 01-010)	Solid tumors	Killing of tumor cells using <i>Salmonella typhimurium</i> bacteria expressing cytosine deaminase gene followed by 5-fluorouracil treatment
<i>3. Immuno-gene therapy for cancer</i>		
EMC (not available yet)	Melanoma	Killing tumor cells by transplantation of autologous T lymphocytes retargeted against major histocompatibility class I and II-restricted MAGE epitopes using a retroviral vector
LUMC (not available yet <sup>#</sup> )	Relapsed hematological malignancies after allogeneic stem cell transplantation	Killing tumor cells by transfusion with virus-specific T cells reprogrammed into leukemia-specific T cells via retargeting to minor histocompatibility antigens using a retroviral vector
NKI (not available yet <sup>#</sup> )	Metastasized melanoma	Killing tumor cells by transplantation of autologous T lymphocytes retargeted against melanoma antigens using a retroviral vector
NKI (not available yet <sup>#</sup> )	HPV-positive penile or cervical cancer	Induction of anti-tumor immune response by vaccination with DNA plasmid encoding the HPV E7 gene
UMCG & AZM & UMCR (IM 06-001/06-003/06-010 <sup>††</sup> )	Metastasized prostate cancer	Induction of anti-tumor immune response by vaccination with two prostate cancer cell lines transduced with AAV encoding the GM-CSF gene (CG1940 and CG8711) compared to treatment with docetaxel and prednisone
UMCG & AZM & AMC (IM 06-001/06-003/06-011 <sup>††</sup> )	Metastasized prostate cancer	Induction of anti-tumor immune response by vaccination with two prostate cancer cell lines transduced with AAV encoding the GM-CSF gene (CG1940 and CG8711) in combination with docetaxel compared to treatment with docetaxel and prednisone
<i>4. Oncolytic adenovirus therapy for cancer</i>		
EMC (not available yet <sup>#</sup> )	Localized prostate cancer	Killing tumor cells prior to surgery by a targeted replicating adenovirus
VUmc (not available yet <sup>#</sup> )	Glioblastoma multiforme	Killing tumor cells by a targeted replicating adenovirus
<i>5. Other gene therapy applications</i>		
AMC (not available yet <sup>#</sup> )	HIV infection and AIDS	Inhibition of HIV replication by HIV-1-specific short hairpin RNAs delivered via a lentiviral vector

# Gentherapie beleid overheid

- Gezondheidsraadadvies “Gentherapie” (1997)
- TNO rapport “Haalbaarheid centrale faciliteit voor vectorproductie” (2000)
- ZonMw programma “Translationeel Gentherapeutisch Onderzoek” totaal budget: 15.6 M€
- Leidraad voor de onderzoeker, april 2007
  - Gezamenlijk loket voor gentherapie van CCMO, VWS en VROM

# Gene Therapy Office and regulatory organisations involved in clinical gene therapy trials in The Netherlands.



# **Gene Therapy Office and regulatory organisations involved in clinical gene therapy trials in The Netherlands.**

- **The Gene Therapy Office**
  - receive and forward the (combined) applications, changes, notifications and reports
- **The Central Committee on Research Involving Human Subjects (CCMO)**
  - Evaluates medical, ethical and scientific aspects of the application. This procedure takes around 90 days.
- **The Ministry of Health, Welfare and Sport (VWS)**
  - approves application in the sense of declaration of no objection which takes 14 days.
- **The Ministry of Housing, Spatial Planning and the Environment (VROM)**
  - Directive 98/81/EC and 2001/18/EC for the environmental risk assessment. This permit is issued within 120 days.
- **The Advisory Committee on Genetic Modification (COGEM)**
  - advises on the application.
- **The European Union (EU) Member States**
  - are informed about the application via publication of the ‘summary notification information format’ (SNIF) form

# **KNELPUNTEN UITVOERING GENTHERAPIE**

- Financiering
- Lange doorlooptijd aanvragen
- Internationalisering
- FDA

