

Regulatory recommendations in Germany concerning the use of retrovirally modified cells

- Clinical gene therapy trials in Germany
- Information on leukemias in France
- Scientific basis for decisions
- Recommendations in Germany

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Clinical gene therapy involving the use of live, retrovirally transduced cells in Germany (1)

- **Treatment of monogenic inherited haematopoietic disease by retrovirally corrected blood stem cells (Chronic Granulomatous Disease):**
Infusion of retrovirally transduced CD34+ stem cells carrying the *gp91phox* gene to correct the underlying immune dysfunction
- **Marker gene transfer:**
Autologous haematopoietic stem cell transplantation: Transfer of retrovirally Δ *Ingfr*- or *neo*- marked stem cells to study haematopoietic reconstitution
- **Multi drug resistance gene transfer:**
Transfer of *mdr* (*multi drug resistance*)-gene into haematopoietic stem cells during blood stem cell transplantation of cancer patient to allow treatment with increased dosages of cytotoxic cancer drugs
- **Suicide gene transfer followed by ganciclovir for GvHD treatment:**
Infusion of donor lymphocytes retrovirally transduced with the *HSV-tk* (suicide) gene to mediate a graft-versus-leukemia effect and treatment of graft versus host disease by subsequent ganciclovir-mediated in-vivo killing of the donor lymphocytes

Blue: On-going before September 2002. Black: Completed (1994 until 2002).

Clinical gene therapy involving the use of live, retrovirally transduced cells in Germany (2)

- **HIV gene therapy:**
Infusion of retrovirally transduced autologous T-lymphocytes or haematopoietic stem cells retrovirally transduced with HIV-inhibitory genes to treat or slow progression to AIDS
- **Treatment of rheumatoid arthritis:**
Transfer of retrovirally transduced synovial cells into joints of patients with rheumatoid arthritis or chronic arthritis (proinflammatory cytokin receptor antagonists, IRAP)
- **Brain cancer therapy by suicide gene transfer/ganciclovir:**
Treatment of glioblastoma multiforme following surgery by inoculation of retroviral vector producing cells (vpcs) mediating suicide gene transfer in vivo

Series of events

- Publication of the Li et al. (2002) paper and confidential information on first leukemia by A. Fischer
- Closed international expert meeting in September 2002. Clinical hold was recommended for all clinical gene therapy trials in Germany involving the use of live, retrovirally transduced cells.
 - September 2002; Paul-Ehrlich-Institut and „Commission for Somatic Gene Therapy“
- Amendments for protocol changes were asked for.
 - Inclusion/exclusion criteria, patient information leaflet, ethical re-consideration.
- The Paul-Ehrlich-Institut was confidentially informed by Alain Fischer about the diagnosis of the second leukemia in December 2002.
- Meeting of the Commission for Somatic Gene Therapy and consultation with Paul-Ehrlich-Institut on 4 February 2003.

Scientific basis for recommendations

- Ethical considerations
 - Age of patients (able to give informed consent or not)
 - Disease (lethal or not)
 - Clinical condition (life-threatening or not)
- Scientific considerations
 - Type of modified cells (blood stem cells or others)
 - Number of modified cells per dose
 - Gene transfer protocol (average vector copy number per cell)
 - Expected level of in vivo expansion (depleted blood cell compartment, selective growth advantage of modified cells)
 - Age of treatment (children <1 year of age or not)

Recommendations since 4 February 2003 by Paul-Ehrlich-Institut and Commission for Som. Gene Therapy

- GvHD trials
(suicide gene transfer into donor lymphocytes):
Continuation
- CGD trial
(„gp91-phox gene transfer into CD34+ cells following mobilisation):
Still on hold, discussion continued in April 2003.
- Rheumatoid arthritis trial
(IRAP gene transfer into synovial cells followed by joint replacement surgery):
May continue pending protocol improvements.
- HIV trial
(HIV inhibitory gene (T20-like) gene transfer into lymphocytes):
To be continued with strict inclusion criteria
(AIDS patients resistant to chemotherapeutic drugs).

