

Liver tumors induced in a single mouse experiment by *in utero* and neonatal lentiviral vector application *in vivo*

Paul-Ehrlich-Institut's commentary of a UK GTAC letter raising concerns about the safety of some lentiviral vectors

On Friday, 05 November 2004, the UK "Gene Therapy Advisory Committee" (GTAC) informed that, during mouse studies on gene therapy of haemophilia, liver tumors were observed following *in utero* and neonatal lentiviral gene transfer *in vivo*. The GTAC expressed its "concerns about the safety of some lentiviral vectors", apparently based on additional information to be released to the public soon. Lentiviral vectors have been derived from immunodeficiency viruses isolated from Humans (HIV) or particular animal species (SIV, EIAV, FIV and others). They transfer into cells not the viral genes, but what is known as therapeutic genes, in this particular case that of blood clotting factor IX, or a marker gene.

Currently, no clinical trials have been performed in Germany using lentiviral vectors neither *in vivo* nor *ex vivo*. In the U.S.A., there is currently a single clinical trial of *ex vivo* lentivirally transduced human autologous T-lymphocytes harbouring an HIV inhibitory gene (*env* antisense gene) applied to a defined cohort of HIV infected persons.

It is known from non-clinical data initially published by Li *et al.* (<http://www.sciencemag.org/cgi/content/full/296/5567/497>) showing leukaemia induction in mice by replication-incompetent retroviral vectors and from the two leukaemia cases observed in the French SCID-X1 („Severe Combined Immunodeficiency, type X1“) gene therapy trial and the recent death of one of these leukaemia patients that replication-incompetent retroviral vectors based on murine leukaemia virus (MLV) may cause tumors under special conditions in mice and in humans. These data were evaluated against information available from many animal and clinical studies using retroviral vectors *ex vivo* which have shown that these vectors can be used safely, at least within up to ten years of treatment

(<http://www.nature.com/cgi-taf/DynaPage.taf?file=/nm/journal/v9/n4/full/nm0403-367.html>). This observation does not exclude long-term effects including tumor

formation. However, there are no general concerns with respect to *ex vivo* retroviral vector use and a number of commentaries published by the scientific community and regulatory bodies have supported this interpretation.

The tumor finding with respect to lentiviral vectors, as communicated by the GTAC, needs rapid and open communication as well as it will need rigorous analysis and publication of the underlying mechanisms. This may include the specific lentiviral vector used, its particular genetic elements, the *in vivo* use and/or route of application and others

(<http://www.nature.com/cgi-taf/DynaPage.taf?file=/gt/journal/vaop/ncurrent/abs/3302417a.html&dynoptions=doi1099997162>). The information about lentiviral vector-associated tumours in a mouse experiment so far marks the first known case of lentiviral vector-associated oncogenesis. A large number of other studies using lentiviral vectors in pre-clinical studies have been undertaken and did not result in tumour formation. On the basis of the data published so far, it is therefore premature to be concerned about lentiviral vectors in general. It is possible, but needs to be proven, that the theoretically known risk of insertional oncogenesis by lentiviral vectors has been practically realized through the experiment that the GTAC is referring to. At this point it can also not be excluded that other causes are underlying the observed toxic effect.

In the CPMP "Position Paper on Development and Manufacture of Lentiviral Vectors (CPMP/BWP/2458/03 Corr)"

(<http://www.emea.eu.int/pdfs/human/press/pos/245803en.pdf>), which has recently been released for comments, the theoretical risk of these vectors to mediate tumour formation is already mentioned. This risk should be taken into account during risk-benefit analysis of clinical trials using integrating vectors in general. **We also refer to the recommendations published by the CHMP Gene Therapy Expert Group at the European Medicines Agency**

(<http://www.emea.eu.int/pdfs/human/genetherapy/538203en.pdf>). **This document recommends, at the current stage of scientific development, the use of retroviral vectors in life-threatening diseases only and after carrying out a rigorous risk-**

benefit analysis before clinical use. In view of the Paul-Ehrlich-Institut, this should also apply to the clinical use of lentiviral vectors.