

RNAi – A new chance for gene therapy?

The RIGHT consortium organised a public panel discussion on ethical aspects of RNA interference (RNAi) based gene therapy at the Berlin-Brandenburg Academy of Sciences and Humanities on the 3rd December 2007. The aim of this meeting was to increase public awareness and to discuss RNAi based gene therapy and the possible new risks and ethical concerns it may raise. The panel discussion was hosted by Thomas F. Meyer, director at the Max Planck Institute for Infection Biology and coordinator of RIGHT, an integrated research project funded by the 6th framework program of the EU with the aim to explore the potential of RNAi in human therapy. Thomas F. Meyer opened the panel discussion and gave a short introduction into the RIGHT project and RNA interference. He was followed by the chair of the panel discussion, Volker Stollorz, a science journalist, who introduced the invited guests and moderated the evening.

The first scientific talk was given by Luigi Naldini (Milan, Italy), co-director of the San Raffaele Telethon Institute for Gene Therapy in Milan and member of the RIGHT Project Coordination Committee. He presented his work on the development of an RNAi-based gene therapy to cure haemophilia B. Haemophilia B is a blood clotting disorder caused by a mutation of the factor IX gene, leading to a deficiency of the factor IX protein. Using a mouse model, Naldini and co-workers inserted a normal factor IX gene in combination with an RNAi based control mechanism to express factor IX gene only in the targeted cells. The promising results raised hopes that this approach could provide a therapeutic tool to cure haemophilia B in humans.

Marina Cavazzana-Calvo, head of the department for biotherapy at the hospital Necker in Paris reported on the first successful gene therapy trial on children with X-linked Severe Combined Immunodeficiency (X-SCID) that was conducted by her group. X-SCID is a profound and severe immunodeficiency characterised by the complete absence of NK cells and T cells in the peripheral blood. This condition has the tendency to induce severe and recurrent infections that are usually fatal in the first years of life. In the trial conducted by Cavazzana-Calvo and co-workers, the group of gene therapy patients had a higher survival rate than the group treated by partially compatible allogeneic stem cell transplantation. However, some of the gene therapy patients developed severe adverse effects including leukaemia and received appropriate treatment. The trial was stopped in due course, but a new trial is likely to start in 2008 with improved experimental conditions. The two following contributions focussed on ethical aspects of RNAi in gene therapy. Christoph Rehmann-Sutter, head of the unit for ethics in the biosciences of the university of Basel and chair of the Swiss national advisory commission on biomedical ethics, provided general ethical consideration on clinical trials, emphasising the explicit responsibility of the

scientific researcher. He further compared conventional gene therapy with RNAi based gene therapy and concluded that even if there are some variations in the details, no new ethical concerns can be raised.

Dietmar Mieth, professor for theological ethics at the university of Tübingen and member of the bio-ethics commission of the German bishops' conference stated that although there are no fundamental ethical objections against gene therapy, several factors should be taken into account when moving from research in the laboratory to clinical applications. Transparency is of particular importance and the hopes that are raised in patients must be considered when introducing new treatments, particularly when a therapy is still in the trial period and a positive outcome is not certain.

A 40 minutes debate followed the individual presentations of the experts during which the panel discussed certain points in more detail. The panel emphasised that there is no difference between pharmaceutical approaches and the application of conventional gene therapy or RNAi based gene therapy in clinical trials and concluded that the same rules for clinical practise must be applied. However, researchers and clinicians should bear in mind that gene therapy attracts more attention than conventional methods which may lead to overreactions when assessing the risks and benefits of such treatments.

A major topic was at what time point to begin a clinical trial. In this respect, the pressure that could be exerted by industry and funding organisations on a scientist to go into clinical trials is of particular significance. Marina Cavazzana-Calvo emphasised the importance of the scientist's independence to give them enough time to evaluate all aspects before moving into a clinical trial, but she also stressed that this is still the case for the vast majority of research in Europe. There are important safety issues to be considered when introducing any new therapeutic approach, but it must also be taken into account that in cases of fatal, yet incurable diseases, lives could be saved with a new therapeutic approach. Transparency is very important and the therapeutic approaches and potential problems must be carefully described to prevent any misunderstanding between the scientist, medical staff, patients, their families and the public.

Volker Stollorz summarised the meeting and concluded that there are no objections with regards to using RNAi in gene therapy if the work is carefully conducted and underlined that RNAi could provide new chances in gene therapy.