Meeting summary
London, May 2013

The EVERREST Consortium had its second face to face meeting in May. This was a really useful opportunity to have a detailed discussion about some complex issues. Anna David, Consultant in Obstetrics and Maternal/Fetal Medicine at UCL and the project's coordinator, started the day by reminding everyone about the different work packages which make up the EVERREST project. This was followed by an update on progress in these work packages. Shirish Joshi, project manager, explained that CiToxLab has been chosen to carry out the reproductive toxicology studies (Work Package 1). Once the contracts are complete Tommi Heikura, research scientist at the University of Eastern Finland, will visit the laboratory to advise on the best way to give the vector.

The EVERREST Team (left to right): Shirish Joshi, Anke Diemert, Jana Brodszki, Maria Sheppard, Richard Ashcroft, Julie Bakobaki, Donald Peebles, Anna Morka, Tommi Heikura, Rebecca Spencer, Sara Sleigh, Anna David, Karel Marsal.

Anna David discussed the choice of gene therapy. There are several different types of vascular endothelial growth factor (VEGF) and there are different gene therapies for some of these different types. The EVERREST project proposes to use Ad.VEGF-$D^{\Delta N \Delta C}$. A version of the chosen vector - Ad.VEGF-$D^{\Delta N \Delta C}$ - with a marker, or FLAG-tag has been used in a clinical trial in patients with heart disease. The evidence from experiments using Ad.VEGF-$D^{\Delta N \Delta C}$ and Ad.VEGF-A_{165}, which has been used in animal studies of FGR, was reviewed by the UK Medicines and Healthcare Regulatory Agency (MHRA) in 2010. They agreed that Ad.VEGF-$D^{\Delta N \Delta C}$ without the FLAG-tag would be suitable for use in the clinical trial.

Dr Rebecca Spencer, Clinical Research Fellow at UCL, discussed the progress on developing the clinical trial (Work Package 3). She explained that the project had

been adopted by the UCL Clinical Trials Unit (CTU) and she would soon be submitting the prospective cohort study for ethical approval. Julie Bakobaki, Clinical Operations Manager at UCL, explained how the CTU would be able to support the trial, providing a Trial Manager and helping to co-ordinate meetings such as the Trial Steering Committee and Data Safety Monitoring Board.

Richard Ashcroft, Professor of Bioethics at Queen Mary and Westfield College, London, gave an update on the bioethics study (Work Package 2). He explained that the literature review had been submitted to the EC on time. This had not discovered any ethical objections to gene therapy *per se* but the psychological impact it may have on women and their partners was very important. In June a post-doctoral fellow, Maria Sheppard, would be starting to interview stakeholders in the partner states. This would be followed by an ethics application submission to carry out interviews with couples who have personal experience of a pregnancy affected by severe fetal growth restriction. The Consortium discussed which patients should be approached for interview.

After the update, the meeting focussed on the clinical trial and prospective study. There were a lot of decisions to be made about how the trial and study would be carried out such as which women should be included, how should they be managed and what information and samples should be collected. Some particularly important issues were how best to occlude the uterine arteries during delivery of the therapy to ensure safety of the mother and fetus, determination of gestational age, differences in diagnosis and management of Fetal Growth Restriction at the European centres and neonatal follow up. Each issue was discussed in detail and will be followed up over the coming months.

To finish Julie Bakobaki explained about the different trial committees, including the Data Safety Monitoring Board, Trial Steering Committee and Trial Management Group. Anna David will be approaching potential independent members of the Trial Steering Committee, which will be responsible for overseeing the trial. The next face to face meeting will take place mid-October 2013 and it was suggested that this should be at one of the other centres.