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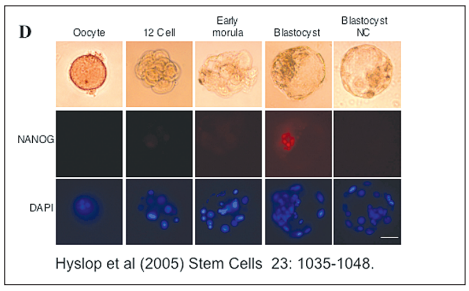
Research Focus

Understanding stem cell pluripotency, self-renewal, survival and differentiation, haematopoietic and corneal lineages

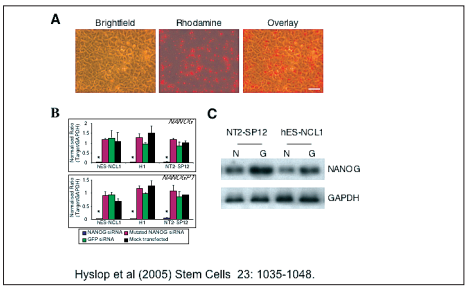
Embryonic stem (ES) cells are able to differentiate into several different cell types and as such, they represent an excellent source of cells for continuous cell replacement therapies, drug discovery and basic biology studies. A key to unlocking this potential is the understanding of the critical pathways and factors that are involved in the maintenance of pluripotency and self-renewal as well as differentiation towards specific lineages. While the molecular basis of tissue differentiation in the mouse embryo is well-appreciated, the molecular mechanisms of human ES pluripotency are poorly understood. In view of this we have embarked on a major research programme to identify key transcription factors and signalling pathways that are necessary for the maintenance of pluripotency, self-renewal and survival in human ES cells with the aim of creating a defined growth medium which will allow the derivation and expansion of ES cells under GMP conditions. Key to the success of our programme has been the successful establishment of RNAi in human ES cells, stable and efficient genetic manipulation of several transcription factors in several ES cell lines and creation of a large number of ES lines with reporter genes driven from promoters of pluripotent genes identified through our large scale transcriptional profiling in nine cell lines.

The second research focus in my group has been the derivation of haematopoietic progenitors from human ES cells with the aim of generating cells that can be used for curing haematopoietic malignancies as well as understanding the very early haematopoietic development. In the last few years we have devised one of the most efficient protocols for obtaining approximately 4500 CFCs/10^5 and shown that haematopoietic niche plays a major role in the induction of embryonic haematopoiesis. Key to the progress of such research to the clinical application will be the scaling up of the differentiation process and understanding of the factors that will enhance the survival of haematopoietic progenitors in culture as well as the site of injury. In this context, we are developing "bioreactor" friendly protocols and investigating the impacts of telomerase expression on the survival and engraftment of ES derived haematopoietic progenitors in collaboration with Prof Shakesheff's group at the University of Nottingham and Dr Saretzki and Prof Zglinicki at the Institute of Ageing and Health in Newcastle.

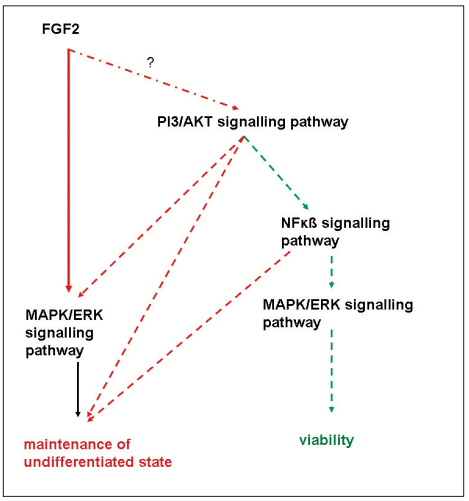
The third research topic relates to identification of new markers for limbal stem cells. This is a joint project running between Dr Sajjad Ahmad, Dr Sai Kollai, Mr Francisco Figueiredo and myself (see page 5).



Expression of NANOG in human embryos.



Downregulation of NANOG by sIRNA.



Important signalling pathways in human ES cells.

Selected publications

Armstrong L., Hughes O., Young S., Hyslop L., Stewart B., Wappler I., Peters H., Walter T., Stojkovic P., Evans J., Stojkovic M and **Lako M.** (2006). The role of PI3K/AKT, MAPK/ERK and NFkß signalling in the maintenance of human embryonic stem cell pluripotency and viability highlighted by transcriptional profiling and functional analysis. Submitted to Human Molecular Genetics, (in press).

Ahmad S, Stewart R, Yung S, Kolli S, Armstrong L, Stojkovic M, Figueiredo F, **Lako M.** Differentiation of human embryonic stem cells into corneal epithelial like cells by in vitro replication of the corneal epithelial stem cell niche. Stem Cells. 2007 Jan 25; [Epub ahead of print]

PMID: 17255521 [PubMed - as supplied by publisher]Armstrong L., Saretzki G., Peters H., Wappler I., Evans J., Hole N., von Zglinicki T and **Lako M.** (2005). "Overexpression of Tert results in enhanced proliferation of murine ES cells, protection from oxidative stress and commitment to haematopoietic lineages" Stem Cells 23:516-29.

Armstrong L., Stojkovic M., Dimmick I., Ahmad S., Stojkovic P., Hole N and **Lako M.** (2004). Phenotypic characterization of murine haematopoietic progenitors on the basis of aldehyde dehydrogenase activity. Stem Cells: 22:1142-1151.

Stojkovic M.*, **Lako, M.***, Stojkovic P., Stewart R., Przyborski S., Armstrong L., Evans J., Herbert M., Hyslop L., Ahmad S., Murdoch A.P., Strachan T. (2004). Derivation of human embryonic stem cells from Day 8 blastocysts recovered after three-steps in vitro culture. Stem Cells: 22:790-7 (* both authors contributed equally).

Lako M., Armstrong, L., Cairns P.M., Harris S., Hole N. and Jahoda C.A.B. (2002). Hair follicle dermal cells repopulate the mouse haematopoietic system. Journal of Cell Science 115:3967-3974.