Professor Jan Frayne
B.Sc.(Nott.), Ph.D.(Bristol)

Professor in Molecular Cell Biology

Area of research

The molecular analysis of erythroid cells generated in vitro from different stem cell sources

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Summary

The generation of RBCs *in vitro* for transfusion therapy is a major goal of health services globally. My research is focussed on the development of *in vitro* systems to generate human erythroid cells from different stem cell sources, including adult, cord and iPSCs, and the molecular analysis of these cells. We utilise innovative proteomic approaches to qualitatively and quantitatively compare the differential proteome of erythroblasts from the different stem cells, along with genetic engineering to alter the behaviour and phenotype. I am also interested in the regulation of erythropoiesis by transcription factors and our studies have revealed both novel transcription factors, and factors differentially expressed in erythroid cells differentiated from some stem cell sources which we are continuing to investigate, alongside downstream effectors. I am particularly interested in the transcritpion factor KLF1 and, in collaboration with Prof Anstee of NHSBT, we were the first to identify and report a mutation in KLF1 that results in a severe human disease phenotype, and to demonstrate how this and other mutations in KLF1 affect DNA binding affinity. More recently an increasing number of individuals with a variety of mutations in KLF1 and varying disease severity have been identified. To study the effect and mechanisms by which these mutations result in disease we are presently developing a human *ex vivo* model system. In addition, we have generated the first human immortalised adult erythroid cell lines, that recapitulate normal erythropoiesis, express normal levels of adult globin and enucleate to form functonal reticulocytes, providing a sustainable supply of red cells. We are now generating further lines and utilising geneome editing approaches to creat sublines with selected genotypes/phenotypes, both for study and as proof of principal for future diagnostics and therapeutics.

Biography

Jan Frayne obtained her first degree from Nottingham University and PhD from Bristol University before commencing research in developmental biology, specifically molecular aspects of spermatogenesis and sperm function. She moved to the Department of Biochemistry at the University of Bristol on a post-doctoral position within this area, obtaining a lectureship here in 2000. Although still maintaining an active interest in this area, in 2004 Jans interests diversified to study of erythropoiesis.

Blood shortage is an important healthcare problem globally, with much interest in generating red blood cells *in vitro* as an alternative to donor blood, with the additional advantage of a safer transfusion product especially for many developing countries. In addition, transfusion requirements for some patients with rare blood group phenotypes cannot be met with present resources.

Jans research initially focussed on the development and utilization of *in vitro* systems to generate human erythroid cells from different stem cell sources (adult, cord blood, induced pluripotent and embryonic stem cells), and the molecular analysis of these cells. She implemented innovative comparative proteomic approaches for these studies, including targeted proteome-wide profiling and identification of transcription factor networks. Data from such studies has provided the most comprehensive insight and catalog to date of the RBC proteome, as well as identifying defects in PSC derived erythroid cells which are presently being targeted. Cord blood stem cells are an attractive progenitor source for the production of RBCs *in vitro* for transfusion. Extensive studies from the Frayne lab addressed the suitability of such cells, reassuring no detectable barrier to their use for adult therapeutics. She also developed a forward programming strategy to induce the switch to, and expression of adult globin by these cells at levels commensurate with normal adult RBCs.

Jan is also interested in the transcription factor regulation of erythropoiesis, identifying novel factors involved in erythropoiesis and lineage fate determination. KLF1 is a key regulator of erythropoiesis, and along with collaborators at NHSBT Bristol, she was the first to identify a mutation in KLF1 that results in a severe human disease phenotype, and demonstrated how this and other mutations in KLF1 can impede function.

Recently, Jan has taken an alternative approach, developing methodology and pioneering creation of the first human immortalised adult erythroid cell line (BEL-A), demonstrating for the first time a feasible approach to the manufacture of red cells for clinical use. The line is also the first erythroid line to recapitulate normal erythropoiesis. Extensive characterization has not revealed any differences between BEL-A reticulocytes and normal adult reticulocytes functionally, or at the molecular level. Genome editing approaches are now being used to create sub lines with specific gene edits as proof of principal for diagnostics and therapeutics. In addition, of particular interest is the use of the methodologies to generate model celular systems of RBC diseases to study the underlying molecular mechanisms and as drug screening platforms.

Jan Frayne is presently a principal investigator for the Bristol Institute of Transfusion Sciences (BITS), for the NIHR Blood and Transplant Research Unit (BTRU) in red blood cell products and for the Wellcome Trust funded BloodPharma (Novosang) consortia to generate RBCs *in vitro* from pluripotent stem cells for therapeutics.

Teaching

Nucleic Acids, Genes and Genomes. DNA Replication, Mutation and Repair

Health Sciences: Biochemistry - Bristol Dental School

Systems case 2 - Cardiovascular

Student choice placement – Molecular and Cellular Basis of Disease

CBL case 4 - Anaemia, blood and clotting

Keywords

- Erythropoiesis
- stem cells
- KLF1
- sperm function

Memberships

Organisations

School of Biochemistry

Other sites

- Medical-school

School of Biochemistry staff

- Biochemistry academic staff

Recent publications

- Trakarnsanga, T, Ferguson, D, Daniels, D, Griffiths, R, Wilson, M, Mordue, K, Andrienko, T, Condie, A, McCahill, A, Mountford, JC, Toye, A, Anstee, D & Frayne, J, 2019, 'Vimentin expression is retained in erythroid cells differentiated from human iPSC and ESC and indicates dysregulation in these cells early in differentiation'. *Stem Cell Research and Therapy*.
- Trakarnsanga, K, Wilson, MC, Heesom, KJ, Andrienko, TN, Srisawat, C & Frayne, J, 2018, 'Secretory factors from OP9 stromal cells delay differentiation and increase the expansion potential of adult erythroid cells in vitro'. *Scientific Reports*, vol 8.
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- Poldee, S, Metheetrairuta, C, Nugoolsuksiri, S, Frayne, J & Trakarnsanga, T, 2018, 'Optimization of an Erythroid Culture System to Reduce the Cost of in vitro Production of Red Blood Cells'. *MethodsX*, vol 5., pp. 1626-1632
- Trakarnsanga, K, Griffiths, RE, Wilson, MC, Blair, A, Satchwell, TJ, Meinders, M, Cogan, N, Kupzig, S, Kurita, R, Nakamura, Y, Toye, AM, Anstee, DJ & Frayne, J, 2017, 'An immortalized adult human erythroid line facilitates sustainable and scalable generation of functional red cells'. *Nature Communications*, vol 8.
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- Perkins, A, Xu, X, Higgs, D, Patrinos, GP, Arnaud, L, Bieker, JJ, Philipsen, S, Frayne, J & , 2016, 'Krüppeling erythropoiesis: an unexpected broad spectrum of human red blood cell disorders due to KLF1 variants'. *Blood*, vol 127., pp. 1856-1862
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PLoS ONE, vol 9., pp. e100874

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