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Development of a Bio-Inspired Blood Factory for Personalised Healthcare

Informe

Información del proyecto

BioBlood

Identificador del acuerdo de subvención: 340719

Sitio web del proyecto

Proyecto cerrado

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Coordinado por
IMPERIAL COLLEGE OF SCIENCE TECHNOLOGY AND MEDICINE
United Kingdom

Este proyecto figura en...

Final Report Summary - BIOBLOOD (Development of a Bio-Inspired Blood Factory for Personalised Healthcare)

BioBlood is an ambitious interdisciplinary project that aims to deliver a “step-change” in precision cellular and drug therapies for patients with blood disorders, specifically those requiring red blood cell (RBC) transfusions and treatments for acute myeloid leukaemia (AML) and chronic lymphocytic leukaemia (CLL). To this end, we have manufactured a 3D hollow fibre perfusion bioreactor (HFB) for the cultivation of human cord blood (CB) and primary human bone marrow (BM) and peripheral blood samples from patients with AML and CLL (for evaluation of treatment). One of the main objectives of the project is to manufacture RBCs for eventual transfusion into patients; the HFB construct has therefore been optimised towards a system which could eventually be used for clinical purposes by (1) 3D scaffold modification using RGD to enhance cell adhesion and growth, (2) improvement of hollow fibres to ensure stability during HFB manufacturing and pore size for selective RBC harvest and, (3) HFB miniaturization in order to achieve normal cell densities using small patient samples. We have successfully cultured CB (in vitro) in long-term serum-free cultures, appropriate for clinical translation, supplemented with near-physiologic cytokine concentrations of only stem cell factor (SCF) and erythropoietin (EPO) in order to harvest RBCs; the 3D HFB supported spontaneous formation of microenvironmental niches and, using a novel mathematical tool (in silico) we developed, the culture process could be divided into two phases: an early “adaptive” phase when microenvironmental niches form, and a later “functional” phase supporting multilineal haematopoiesis. The 3D culture was further optimised towards physiologic erythropoiesis, by using a combination schedule of early low oxygen (hypoxia) exposure with late normal oxygen (normoxia) exposure. Using this 3D culture, unique microenvironmental niches for red cell maturation and novel tools to identify human erythroid developmental stages were created; re-seeding the culture at 4-5 weeks and an EPO spike successfully enhanced erythropoiesis to 8 weeks in serum-free and cytokine-free conditions. The second main objective of BioBlood is to create a 3D culture (in vitro) and mathematical model (in silico) of human AML and CLL throughout treatment. Using primary patient samples, long-term 3D static serum-free and cytokine-free cultures of AML and CLL have been achieved. In order to investigate the role of the microenvironment and parameters for the bioprocess, a metabolomics protocol has been established for primary and cultured AML samples, results for which have highlighted the importance of glycolysis in AML. An in silico model of CLL disease progression was created and has identified that proliferation of CLL in BM and lymph nodes and the migration rates between them are critical targets. In order to achieve precision, we have developed an in silico Population Balance Model

(PBM) which incorporates experimentally-derived cyclin parameters within the mathematical description of the cell cycle to describe leukaemic heterogeneity and kinetics. Using PBM and experimental validation with leukaemia cell lines, we have been able to predict leukaemic clonal kinetics over time and derive clonal origins. An extended dynamic in silico PBM model, “πChemo”, integrates patient and disease parameters at diagnosis, pharmacokinetics-pharmacodynamics, growth kinetics and leukaemic cell cycle parameters with heterogeneity defined by the PBM for both normal and diseased BM cells. Retrospective patient datasets in AML were used to validate πChemo, which could capture disease kinetics, response to treatment and normal neutrophil recovery over the entire course of chemotherapy for both intensive and non-intensive chemotherapy regimens. Chemotherapy schedule and dose could be optimised for improved efficacy and reduced toxicity. Integration of πChemo with an immune module has enabled the validation of outcomes for patients treated with combination chemo-immunotherapy. We are now planning a prospective clinical trial to assess whether the in silico πChemo platform and the in vitro disease modeling in 3D culture can be predictive of in vivo patient responses to therapy.

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