Deciphering the role of fibroblasts and macrophages in bone marrow mediated chemotherapy resistance in acute myeloid leukaemia

Mark Williams[1,2], Barbara McCrorie[1], Abigail Macleod[1], Scott Davidson[2], Gregor McMurray[3], Chris Estell[4], Joanne Hanney[5], Carl Goodyear[6], Gerard Graham[6], Helen Wheadon[6] and **Monica Guzman[7]**

[1]Glasgow Caledonian University, UK
[2]University of Strathclyde, UK
[3]NHS Greater Glasgow and Clyde, UK
[4]University of Exeter, UK
[5]NHS Ayrshire and Arran,
[6]University of Glasgow, UK
[7]Cornell University, USA

Acute Myeloid Leukaemia (AML) is one of the most pressing unmet clinical need in the haematology field. For the majority of AML patient's survival is between 5-20%. Chemoresistance is a major contributing factor towards inferior survival in AML, which is significantly influenced by the bone marrow microenvironment (BMME). Within the BMME, AML cells interact with stromal (e.g. fibroblasts) and immune cells (e.g. macrophages [Mϕs]), with a well-established role for these cells impacting upon chemoresistance in blood cancers, including Multiple Myeloma.

The study objectives were to ascertain the role played by fibroblasts and Mϕs in conferring protection of AML cells from cell death induced by traditional chemotherapeutics and a multi-cyclin-dependent kinase/myeloid cell leukaemia 1 inhibitor (multi- CDKi/MCL1 i) AML cells and determine the molecular mechanism(s) underlying this chemoresistance.

U937 cells were incubated with normal media (NM) or conditioned media from the human BM fibroblast cell line HS5 (HS-CM) or primary Mϕs (Mϕ-CM). The U937 cells were then exposed to daunorubicin/doxorubicin (1mM) or the multi-CDKi/MCL1i (0-10 mM) for 24h. HS-CM and Mϕ-CM significantly protected U937 cells from the effects of the daunorubicin/doxorubicin and the multi-CDKi/MCL1i. HS-CM and Mϕ-CM activated various pro-survival and anti-apoptotic pathways in U937 cells including the ERK1/2 and MCL-1 pathways respectively. Initial studies suggest that treatment of U937 cells with the MEK1/2 inhibitor selumetinib re-sensitised the U937 cells to the multi-CDKi/MCL1i in the context of HS-CM.

These findings demonstrate that combining a novel multi-CDKi/MCL1i with selumetinib may overcome fibroblast elicited chemoresistance and may represent a promising therapeutic approach for AML.

Speaker Biography

Mark Williams qualified with a BSc (Hons) in immunology and pharmacology from the University of Strathclyde in 2006. He was then awarded a PhD in immunobiology from Queen's University Belfast in 2010, where he conducted studies investigating the impact of different CFTR mutations on inflammation in cystic fibrosis. He then conducted his postdoctoral research studies in acute lymphoblastic leukaemia and multiple myeloma at the University of Glasgow from 2010-2016. He obtained his lectureship in cell and molecular biology at Glasgow Caledonian University in 2017, in which his research focuses on modelling and therapeutically targeting leukaemia-bone marrow microenvironment interactions in acute myeloid leukaemia. He has published papers in high impact journals including blood and he is also a reviewer for the open access Journal Cancer Drug Resistance, as well as research grants for the Glasgow Children's Hospital Charity and the Carnegie Trust.

e: mark.williams@gcu.ac.uk

Notes: