Using a multi-omics approach to investigate the reversal of proteasome inhibitor drug resistance in multiple myeloma with epigenetic inhibitors

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A thesis submitted for the degree of Doctor of Philosophy

Trinity 2021

Abstract

Background: Multiple myeloma (MM) is an incurable cancer of plasma cells. Novel therapeutics, including proteasome inhibitors (PI) and immunomodulatory imide drugs, have almost doubled median survival time of MM patients. However, most patients relapse and become resistant to drugs they previously have been treated with. Acquired anti-cancer drug resistance remains one of the biggest barriers in the treatment of myeloma.

Aims: PI resistance mechanisms in MM will be investigated with the aim of reversing the resistance phenotype, making MM cells sensitive to proteasome inhibition. Standardised robust wet-lab and computational single-cell workflows will be established to characterise drug-resistant MM cells and their surrounding microenvironment at different points in disease progression.

Results: Cured cancer mate

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Acknowledgements

I would like to thank my supervisors Dr Adam Cribbs, Professor Udo Oppermann and Dr Sarah Gooding for all of their help and guidance throughout my DPhil. I would also like to thank Dr James Dunford, Dr Martin Philpott, Dr Filiz Sengabobulo for all of their help and knowledge in the wet lab. Professor Kessler's lab including Darragh, Adan

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 ${f RNA ext{-}Seq}$. . . Ribonucleic acid sequencing

 $\mathbf{scRNA} ext{-}\mathbf{Seq}$. . Single cell RNA-Seq

 \mathbf{MM} Multiple Myeloma

Introduction

1.1 Introduction to multiple myeloma

Multiple myeloma accounts for 1-2% of all cancers and has the second highest incidence of hematological malignancies, after non-Hodgkin's lymphoma [1].

1.2 Treatment of multiple myeloma

Historically multiple myeloma..

- 1.3 The ubiquitin-proteasome system
- 1.4 Drug resistance in multiple myeloma
- 1.5 Introduction to epigenetics

2 Background

- 2.1 Drug resistance in MM
- 2.1.1 Genomic changes in drug resistant MM
- 2.1.2 Epigenetic changes in drug resistant MM

Appendices



Epigenetic compound screen

A compound screen consisting of approximately 140 epigenetic inhibitors was performed for AMO-1 cells.

References

[1] International Myeloma Working Group. "Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group". In: *British journal of haematology* 121.5 (2003), pp. 749–757.