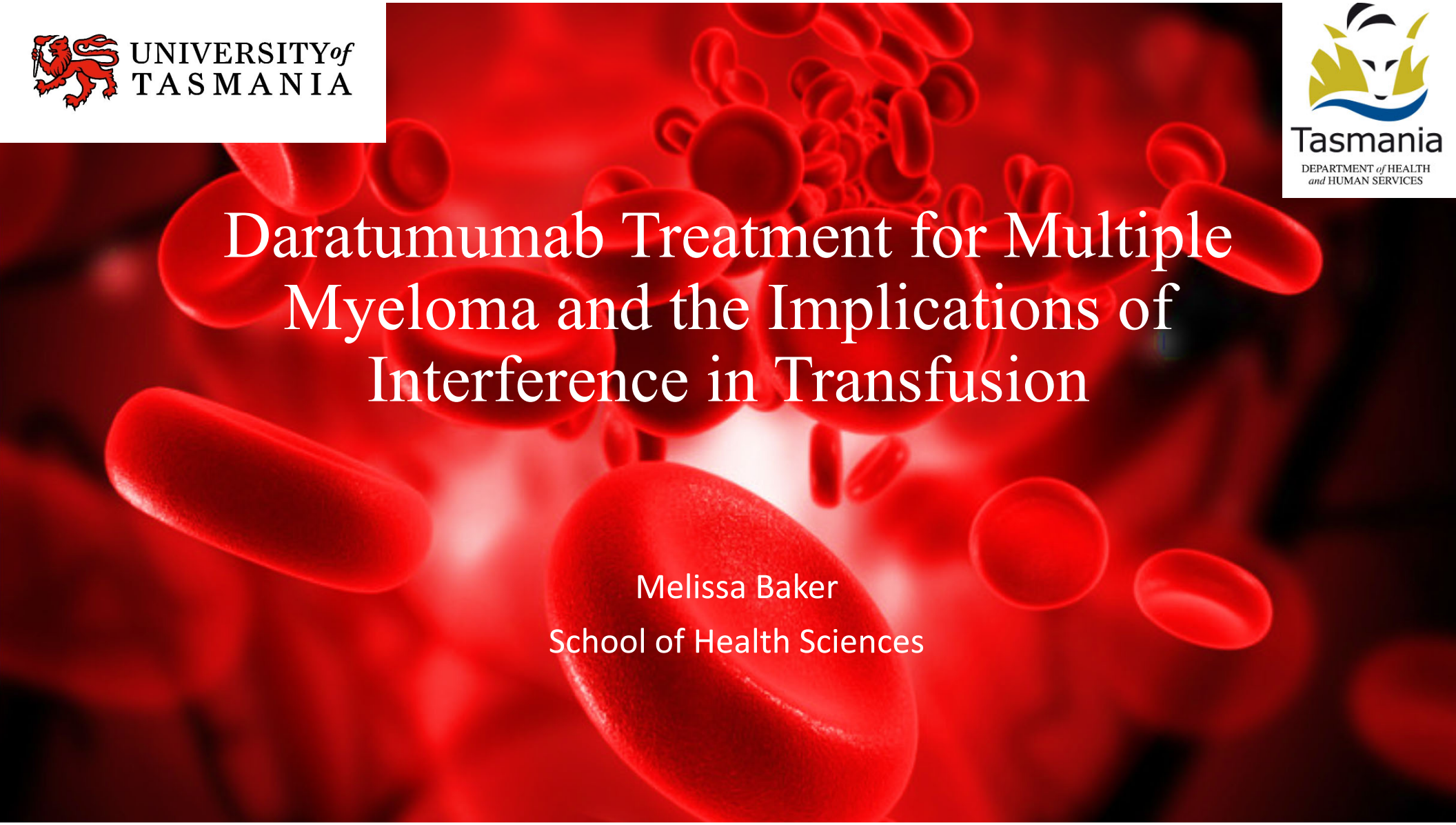

Daratumumab Treatment for Multiple Myeloma and the Implications of Interference in Transfusion

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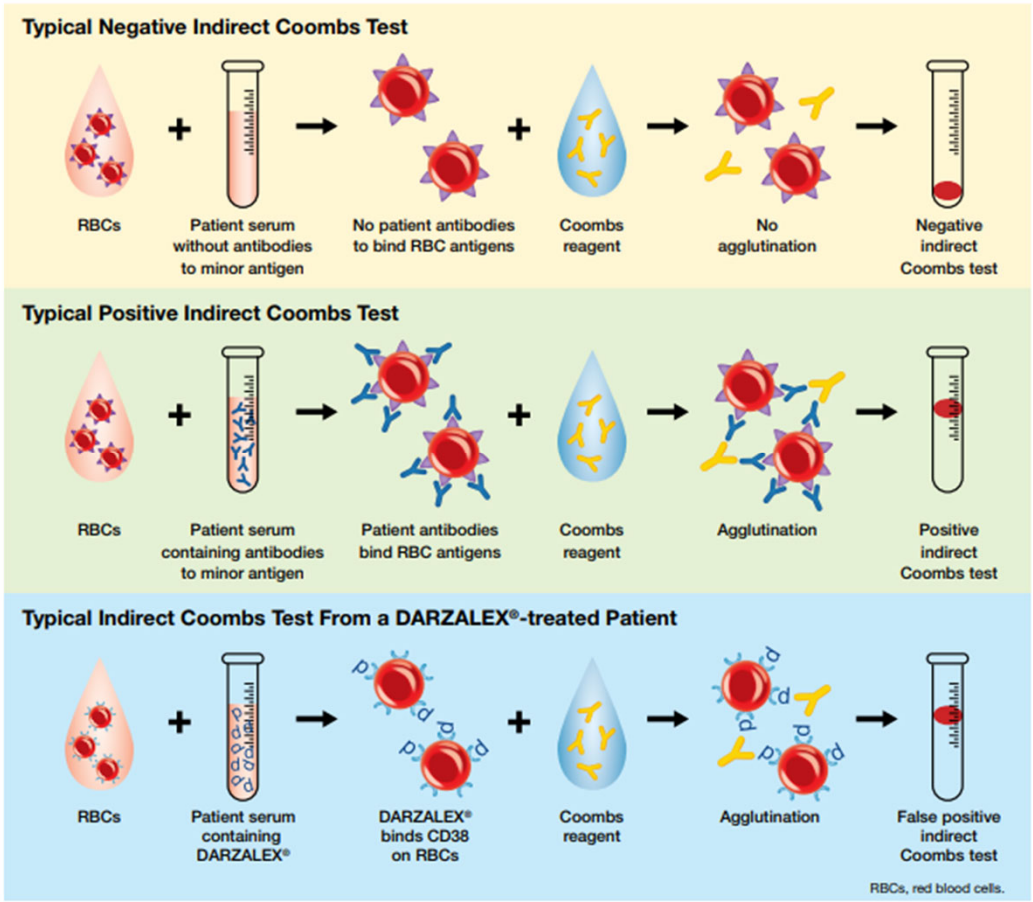
Daratumumab

- Daratumumab is an immunoglobulin G1 kappa (IgG1k) human monoclonal antibody (MoAb)[1]
- Approved by the Australian Therapeutic Goods Administration for the treatment of relapsed/refractory multiple myeloma (MM) in July 2017[2]
- Available to MM patients who have received at least three prior lines of therapy including an immunomodulatory agent and a proteasome inhibitor or who are double refractory to both [1, 3]
- Daratumumab specifically targets the integral transmembrane glycoprotein CD38 highly expressed on plasma cells[4]
- Daratumumab has anti-myeloma activity through CD38-mediated immune mechanisms[2]

Patient Implications of Daratumumab

- Anaemia, neutropenia and thrombocytopenia are common due to CD38 glycoprotein expression on other haematopoietic cells
- Daratumumab related immune-mediated haemolysis has not been reported in these patients [2]
- Nausea and fatigue are frequent adverse effects of daratumumab treatment[5, 3]
- Serum protein electrophoresis and immunofixation assays used for the clinical monitoring of M-protein's produced by MM plasma cells are impacted by daratumumab[5, 3]
- The presence of CD38 on the surface of red blood cells leads to complications in transfusion testing.

Transfusion Implications of Daratumumab

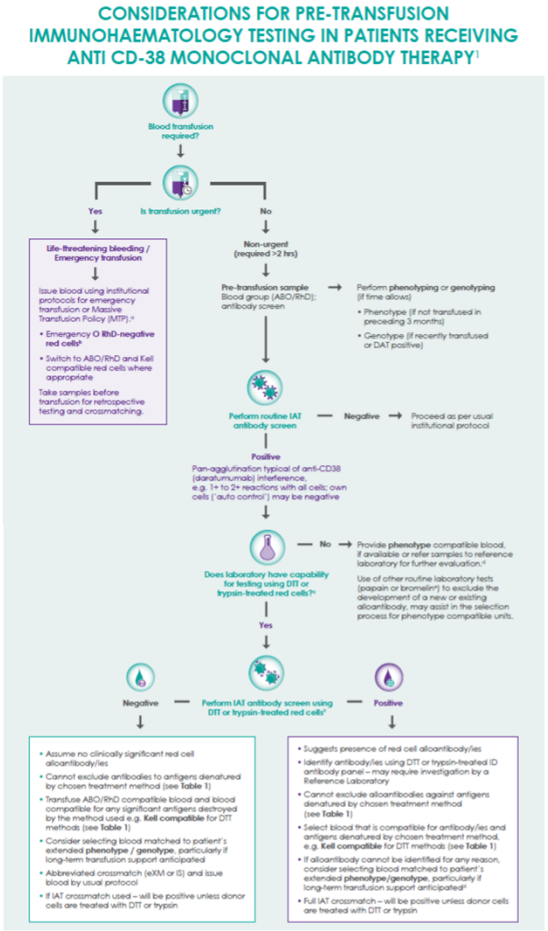


https://www.darzalexhcp.com/sites/www.darzalexhcp.com/files/darzalex-information-on-assay-interference.pdf

How to Alleviate Daratumumab Interference

- Dithiothreitol (DTT) treatment of reagent RBC's
- DTT treatment fails to detect antibodies to Kell, Cartwright, Indian, JMH, Scianna, LW, Lutheran, MER2, Ge3, Dombrock, Diego and Cromer antigens as they are either denatured or weakened by DTT treatment [1, 2]
- Extended RBC phenotyping or genotyping prior to first Daratumumab dose.
- Provide phenotypically or genotypically matched RBC units to minimise the risk of sensitisation and alloantibody formation[1, 2].
- Neutralize daratumumab with soluble CD38 antigen or CD38 anti-idiotype antibody[1, 2] - Routinely unavailable.

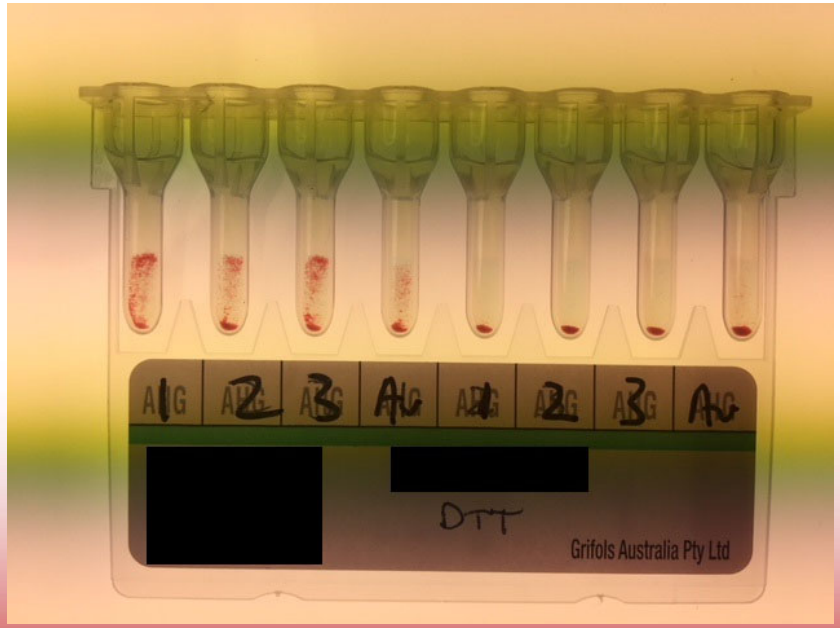
ANZSBT Guideline



https://www.anzsbt.org.au/data/Pre-transfusion_Immunohaematology_testing_cd38_blood_typing_guideline_chart_-_web_version_May_2018.pdf

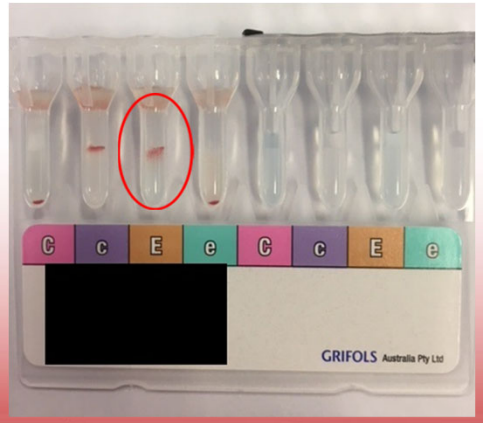
First Attempt of DTT Treatment

- Untreated screening cells and auto-control vs DTT treated screening cells and auto-control.



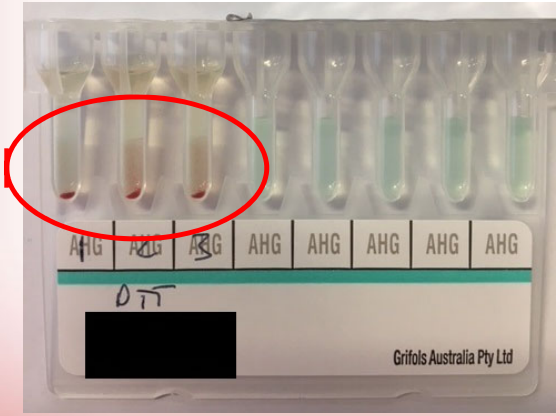
Has DTT Treatment Been Effective????

- Treatment of control RBC's is required to validate the DTT treatment performed on panel cells used in the IAT on the patient plasma.
- Positive control cells include Rhesus E (E+E+) or (E+e)[6].
- Negative control cells include Kell (K+K+) or (K+k-)[6].
- Control cells are either homozygous or heterozygous however to avoid the possible effects of dosage homozygous cells are best for validation of the DTT method.

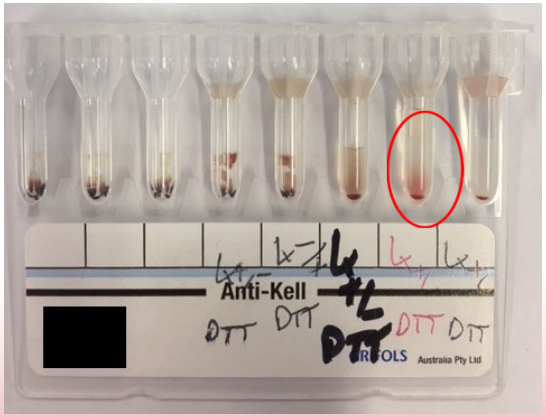


Challenges of the DTT Method

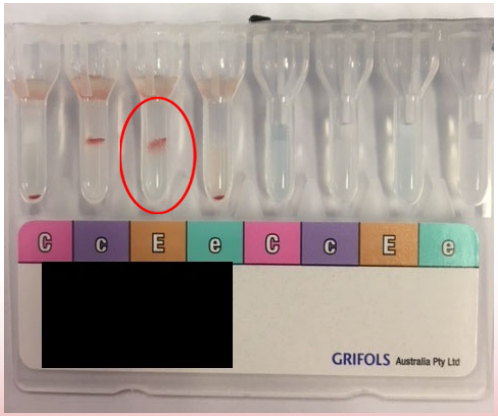
- Proceeding treatment revealed panagglutination of the DTT treated panel cells
- The negative control also displayed panagglutination indicating unsuccessful DTT treatment.



DTT Treated Screening cells 1, 2 & 3



Negative Control



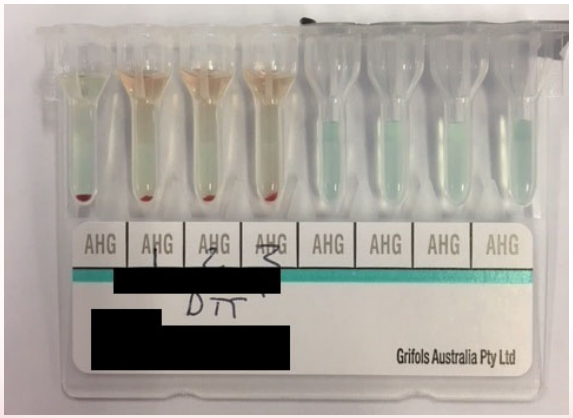
Positive Control

Steps Followed to Overcome DTT Challenges

1. Washed panel cells in a more thorough manner following DTT treatment
2. Refreshed the buffer
3. Increased incubation times of the DTT treatment from 30 mins up to an hour.
4. Increased the DTT concentration from 0.2mol/L to 0.25mol/L
5. Changed RBC:DTT volumes from 100ul:400ul to 200ul:800ul
6. Changed the RBC:DTT ratio from 100ul:400ul to 100ul:800ul
7. Sourced a new set of CSL panel cells from the supplier

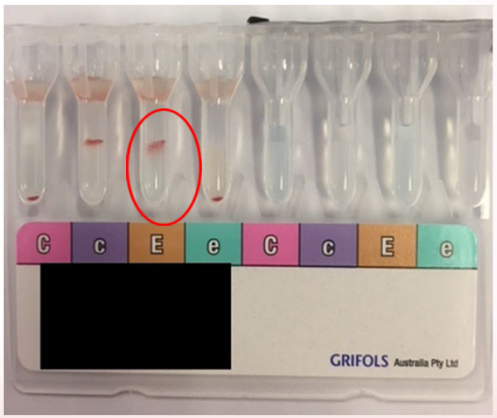
DTT Treated Fresh Panel Cells

- DTT treatment of fresh panel cells alleviated the panagglutination and is validated by both positive and negative controls.



Auto-Control & Screening cells 1, 2 & 3

Negative Control



Positive Control

Current Point of DTT Method Development

- The DTT method was repeated using the new CSL panel cells however panagglutination resulted.
- Current theory is deterioration of the reagent RBC's.
- LGH method still under development following the guidance of the ANZSBT guidelines, advice from The Australian Red Cross Blood Service and reagent supplier Immulab.

- Some laboratories might call this **'probably negative'** against the pre DTT results……..would you put your name to it??!!

Acknowledgements

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