Quantifying the importance of target organ specific interactions in the aetiology of GVHD

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Graft versus host disease

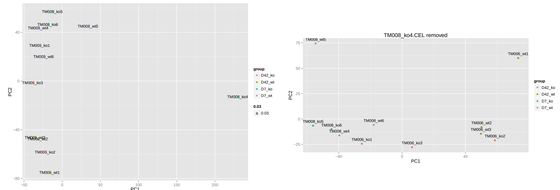
- In malignant pathologies the donor immune system recognises tumour cells as foreign and eradicates them via immunological mechanisms which together are known as the graft vs tumour (GVT) effect
- Donor immune cells may also attack normal host tissue resulting in acute graft vs host disease (GVHD)
- The skin, liver and gastrointestinal tract are the most common tissues to be damaged in GVHD
- GVHD remains one of the most common post-transplant complications and represents a major barrier to the successful application of allo-HSCT
- A major risk factor involved in GVHD pathology is the use of HLA-mismatched, non related donors
- Acute GVHD involves alloreactive donor T-cell mediated cytotoxic response to the tissues of the recipient
- Tissue damage caused by cytotoxic T cells leads to recruitment of other effector cells including natural killer cells which further increases tissue injury and results in self perpetuating GVHD
- Mice represents the primary model animal for pre-clinical studies of GVHD
- Mouse models of acute GVHD usually involve a bone marrow transplant (BMT) which is supplemented with varying numbers/types of donor lymphocites into irradiated allogenic recipients who differ from donors in their MHC class 1 and/or class 2 molecules or in minor histocompatibility antigens

The ImmGen project

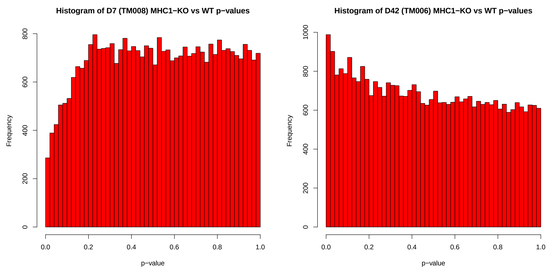
- The primary aim of ImmGen project is to be comprehensive definition of gene expression and regulatory networks in cells of the mouse immune system
- Genes are grouped into modules according to similarities in expression profiles
- Immgen coarse modules consist of groups of genes with broadly similar expression profiles while fine modules represent more defined collections of genes with a high degree of similarity in the expression patterns
- By comparing differentially expressed gene sets to ImmGen, it is possible to identify expression level changes of potentially biologically relevant pathways within the data

T-cell expression in multiple minor histocompatibility antigen-mismatched BMT model

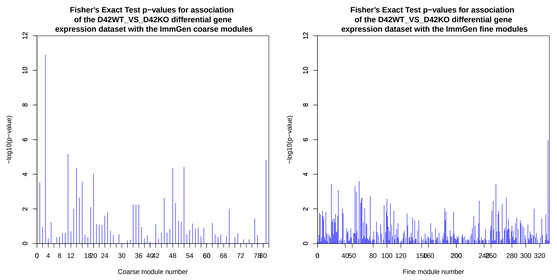
Objective: In a polyclonal model, evaluate the differences in gene expression of effector T cells found in the lymphoid organs or in the peripheral tissues through the use of MHC1 knock out mice



- As shown in the left plot, PCA analysis of all samples reveals presence of outlier in the D7 dataset (***TM*008$_k$*o4***)
- Decision was made to remove this sample for further analysis in the hope of obtaining more reliable and biologically relevant data



- Histogram of the D7 P-Values does not include outlier sample
- A dip in the plot at low P-Values is visible, this is inconsistent with a uniform distribution of P-Values under the null hypothesis
- The reason for this unusual distribution is still not clear - the RMA package used in this analysis may be a factor but this is currently under investigation

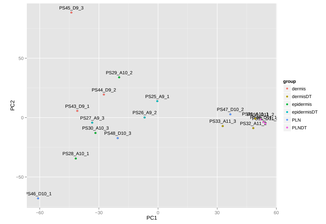


- Above graphs show the relative associations of the D42 data set with the immgen database, the D7 plots show no significant associations and so are not included here
- Significant associations seen for Coarse module 3 and Fine module 332

Coarse module 3 most significant differentially expressed genes		
gene name	fold change	pvalue
Ptbp2	0.8575669378	0.0002380649
Trappc1	-0.8105321657	0.0011522667
Mrpl32	-0.9482075354	0.0015174569

T-cell expression: Single minor histocompatibility antigen-mismatched BMT model

Objective: In a monoclonal model, evaluate the effect of depleting Langerhans cells on the gene expression of effector T cells found in the lymph nodes and in the skin.



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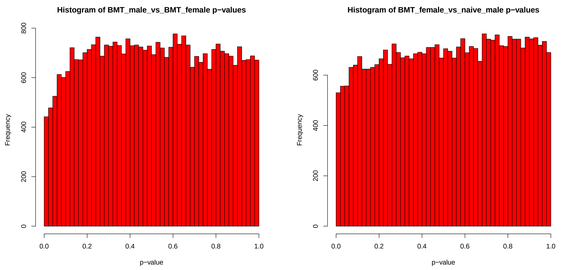

- Histogram of BMT male vs naive male p-values appears to show a more consistent distribution with the null hypothesis
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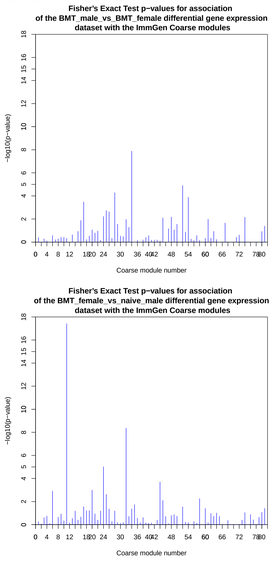
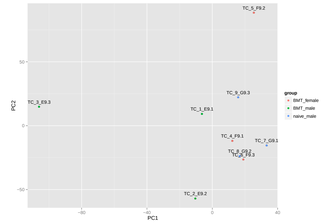


Coarse module 34 differentially expressed genes		
gene name	fold change	pvalue
Gbp5	-1.9977876921	0.000035098
Nlrc5	-1.921796943	0.0008103697
Foxp4	-1.2158361089	0.0218969258
Clec2D	-1.0375138397	0.0068116015
Cblb	-0.9141390753	0.0055652566
Tap1	-0.8921599554	0.0110426477

Coarse module 11 differentially expressed genes with greatest fold changes		
gene name	fold change	pvalue

Langerhans cell expression

Objective: Evaluate the differences in gene expression of Langerhans cells in the setting of an allogeneic BMT or a syngeneic BMT.



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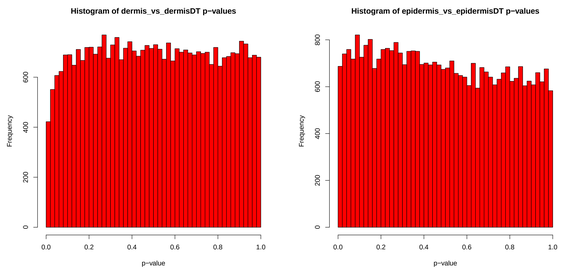

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