

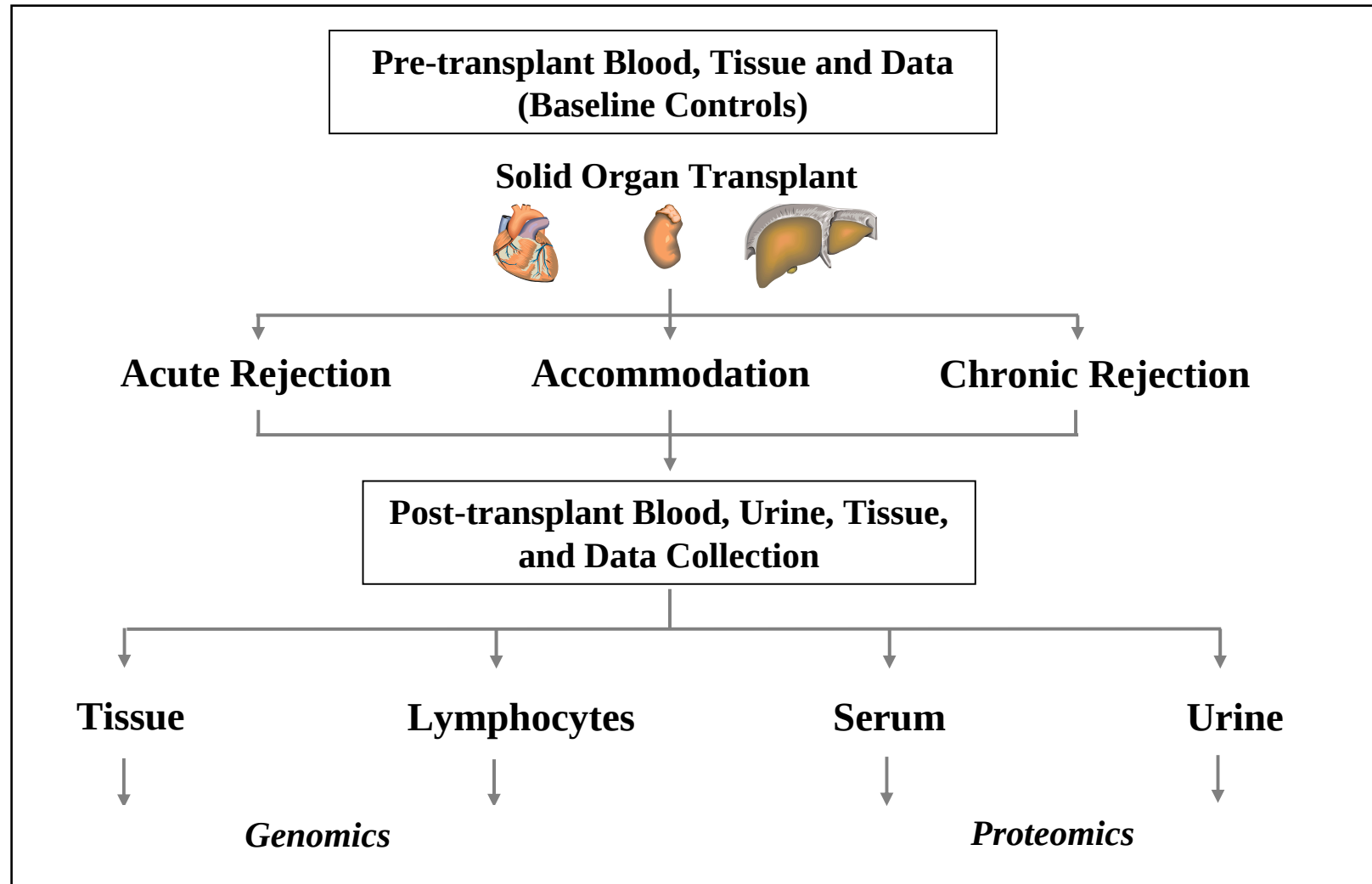


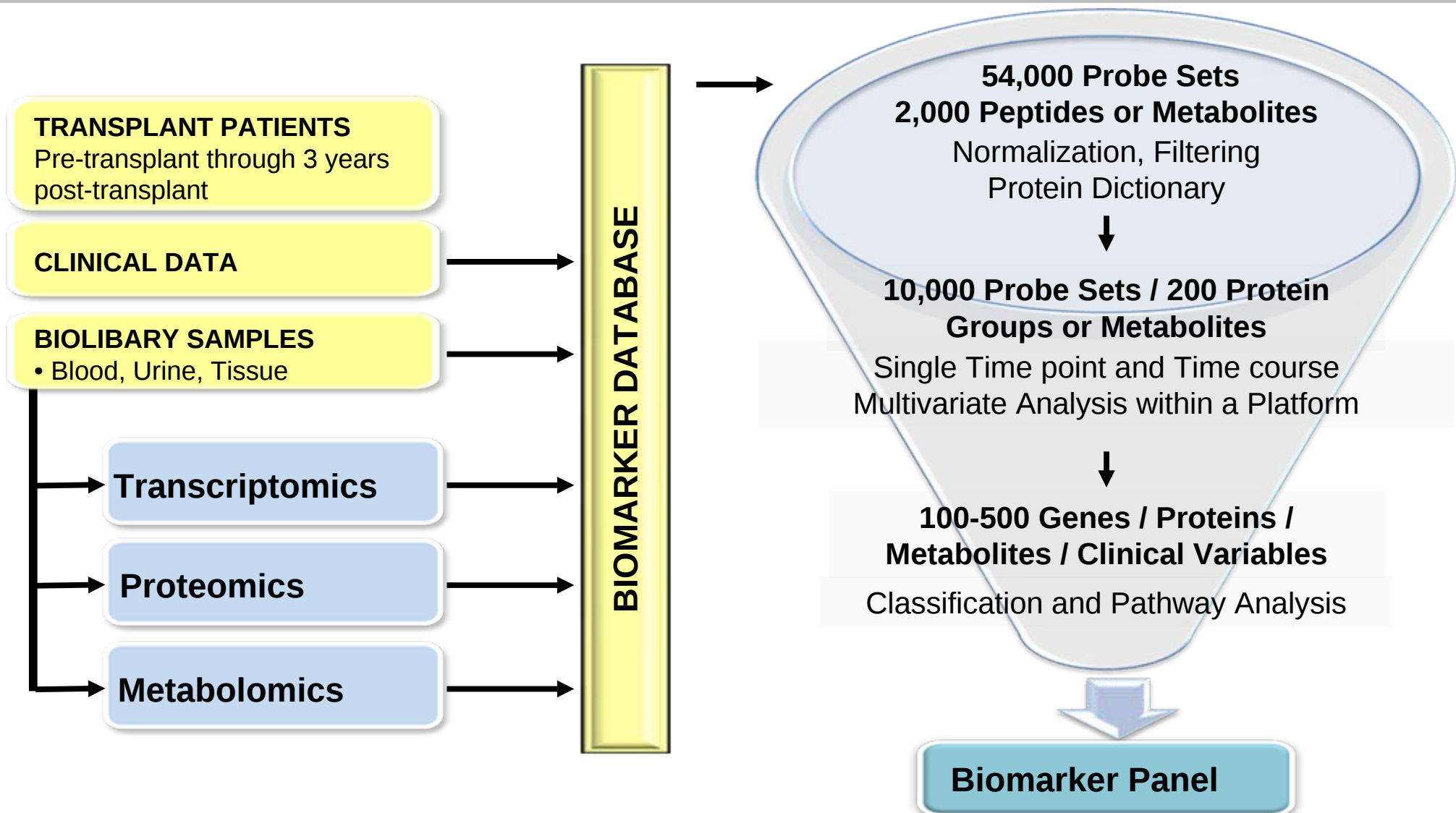
Biomarkers in Transplantation Genome Canada Program

University of British Columbia
Departments of Medicine and
Pathology and Laboratory Medicine

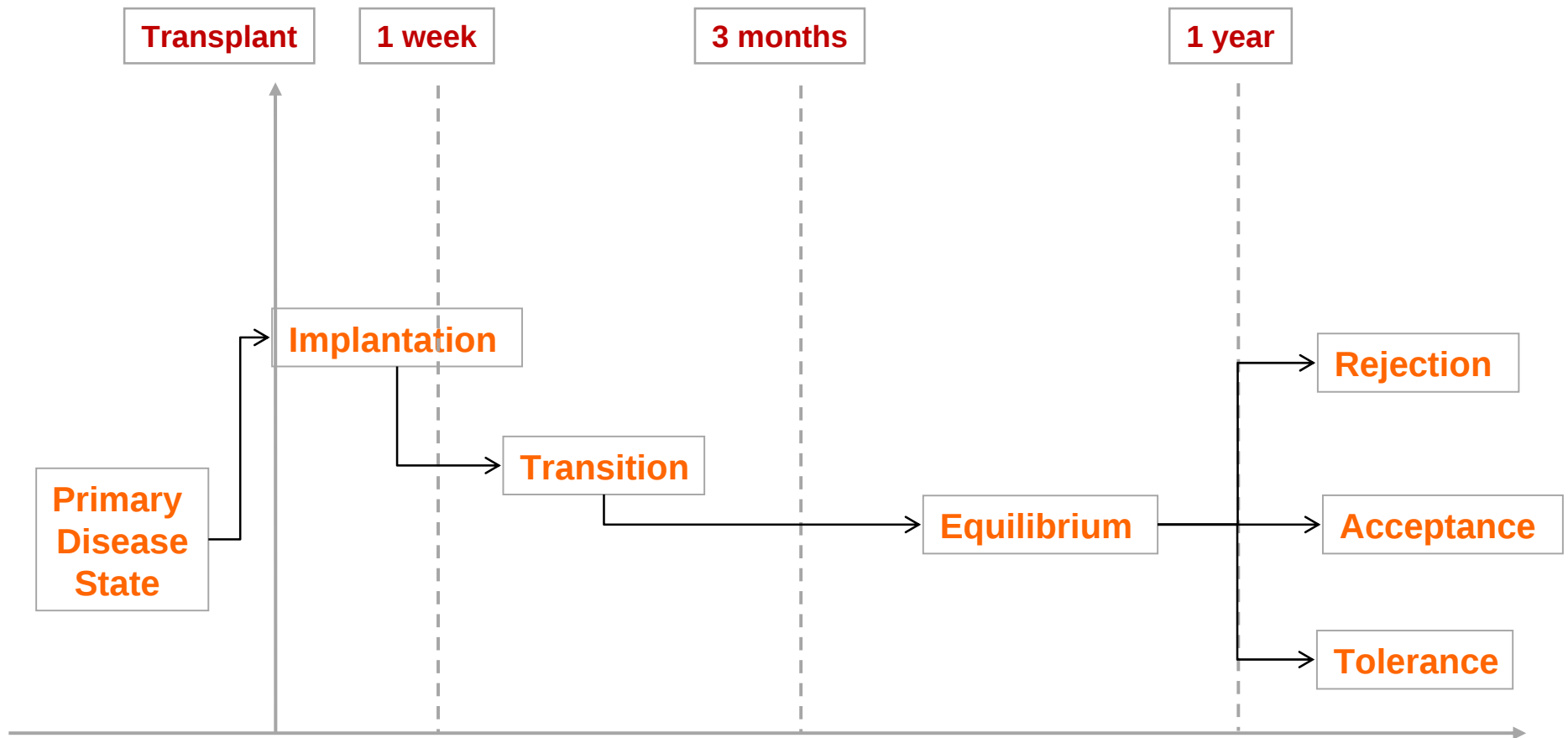
P.Keown MD, DSc, FRCP, FRCPC

- **Acute Rejection** –acute immune attack with cellular or antibody mediated injury and associated inflammation
- **Chronic Rejection** – persistent immune attack with injury, repair, remodeling, fibrosis and failure
- **Accommodation** – immune acceptance of the transplanted organ maintained by immunosuppression
- **Tolerance** – immune acceptance of the transplanted organ comparable to the recipient's own tissues

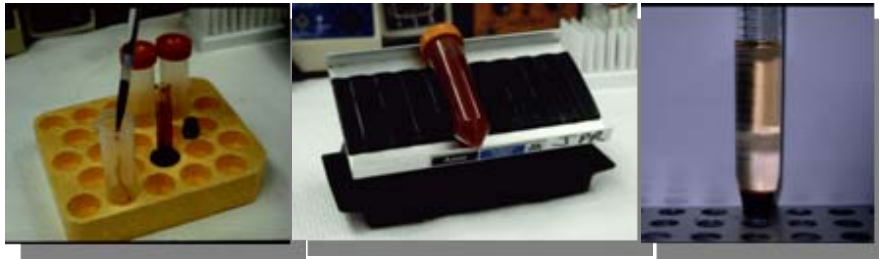




		Total	De Novo	Existing
Total Number				
	Patients enrolled	562	459	103
	Timepoints collected	3761	3649	112
	Samples available	23045	22302	743
Number of Kidney Transplants				
	Patients enrolled	407	335	72
	Timepoints collected	2713	2637	76
	Samples available	16351	15854	497
Number of Heart Transplants				
	Patients enrolled	63	48	15
	Timepoints collected	410	390	20
	Samples available	2832	2693	139
Number of Liver Transplants				
	Patients enrolled	92	76	16
	Timepoints collected	638	622	16
	Samples available	3862	3755	107



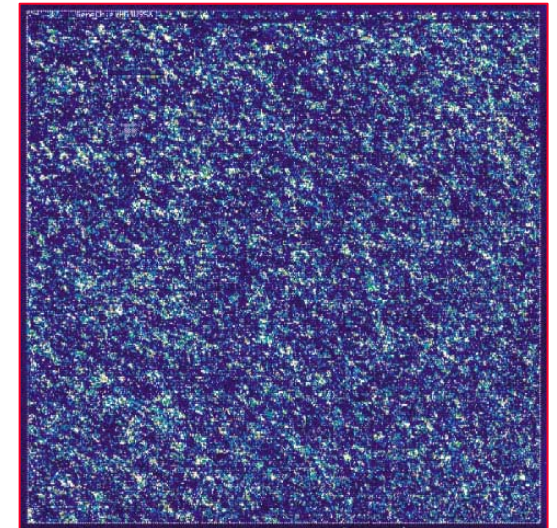
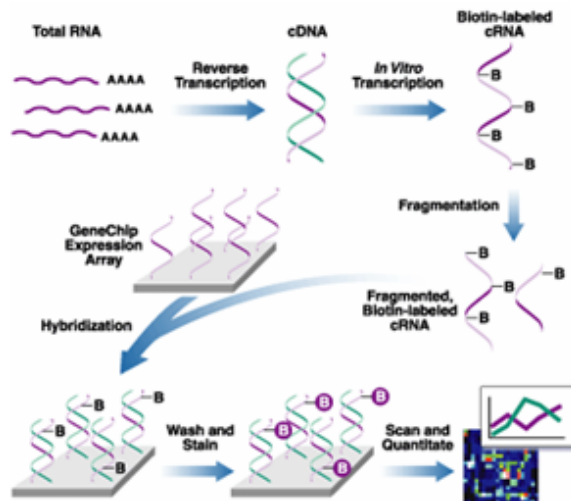
1.



2.

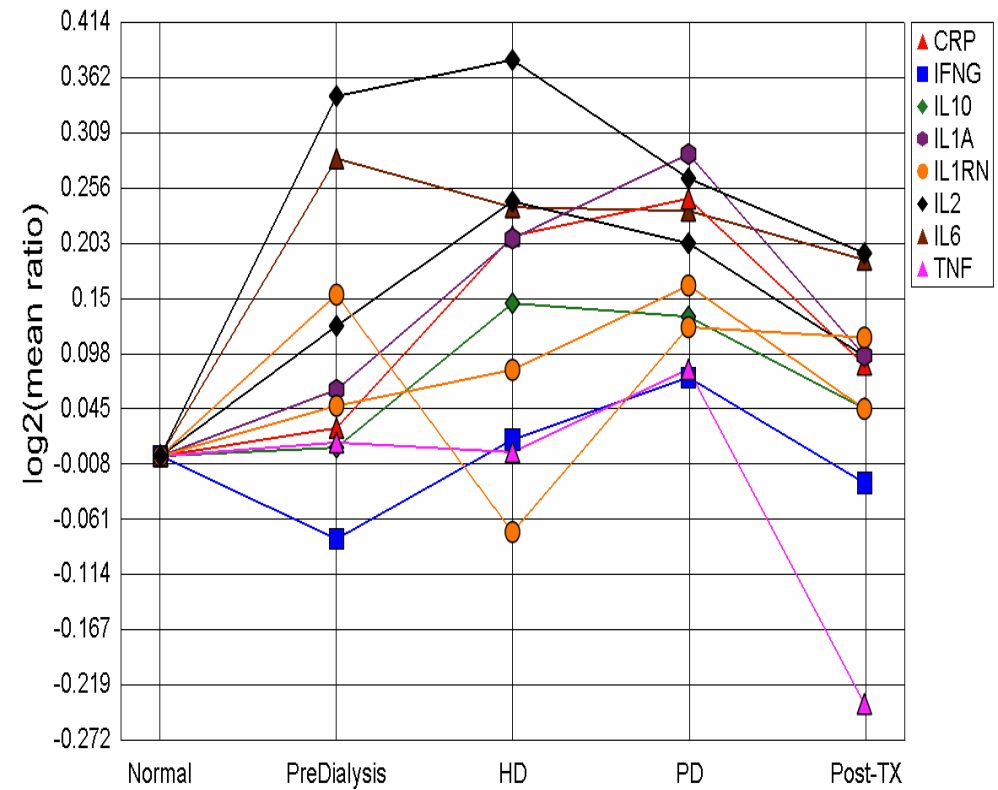
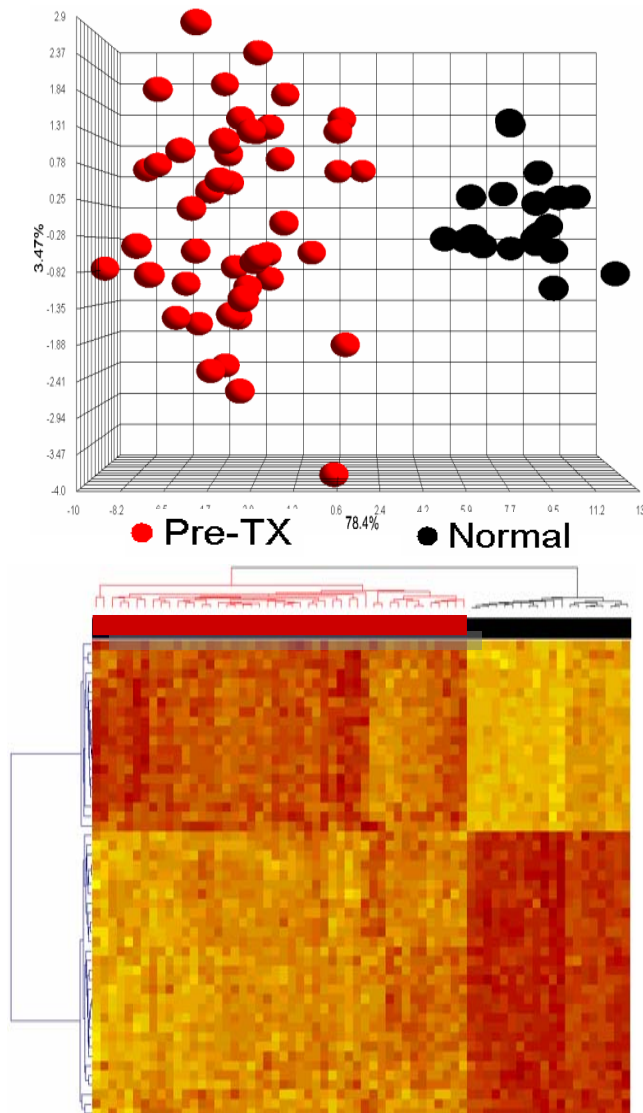


3.



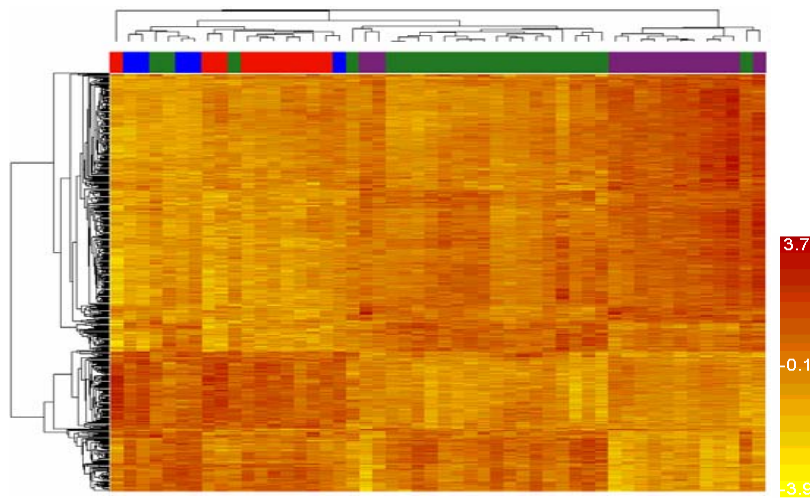
CST

GENE TRANSCRIPTS AND INFLAMMATION IN UREMIA



CST

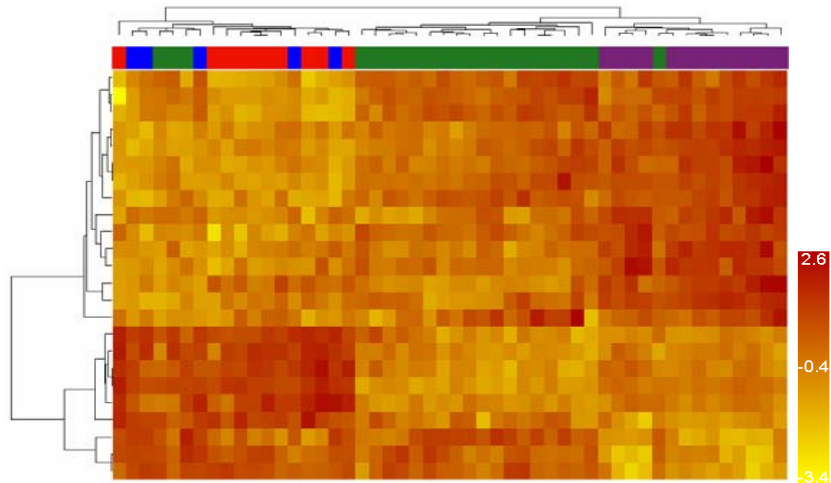
DIFFERENTIAL EXPRESSION BY TREATMENT MODALITY



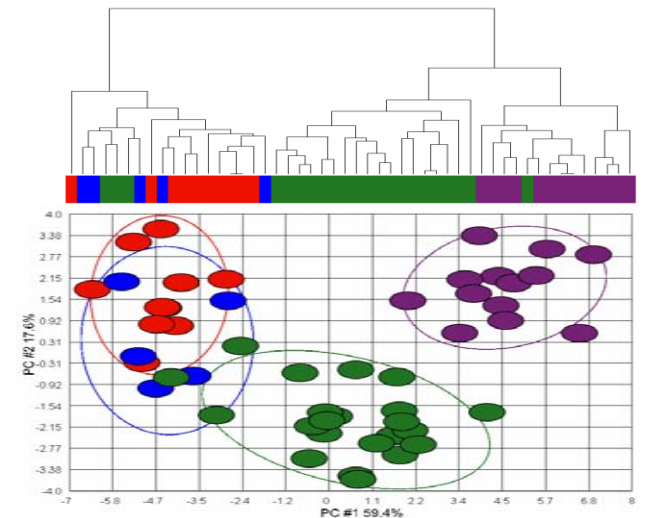
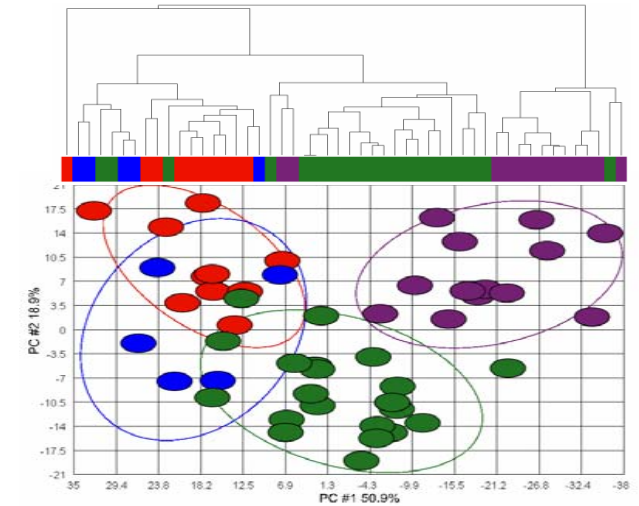
DIALYSIS_TYPE

- CAPD
- CCPD (Automated PD)
- Conventional Haemo
- Pre Dialysis

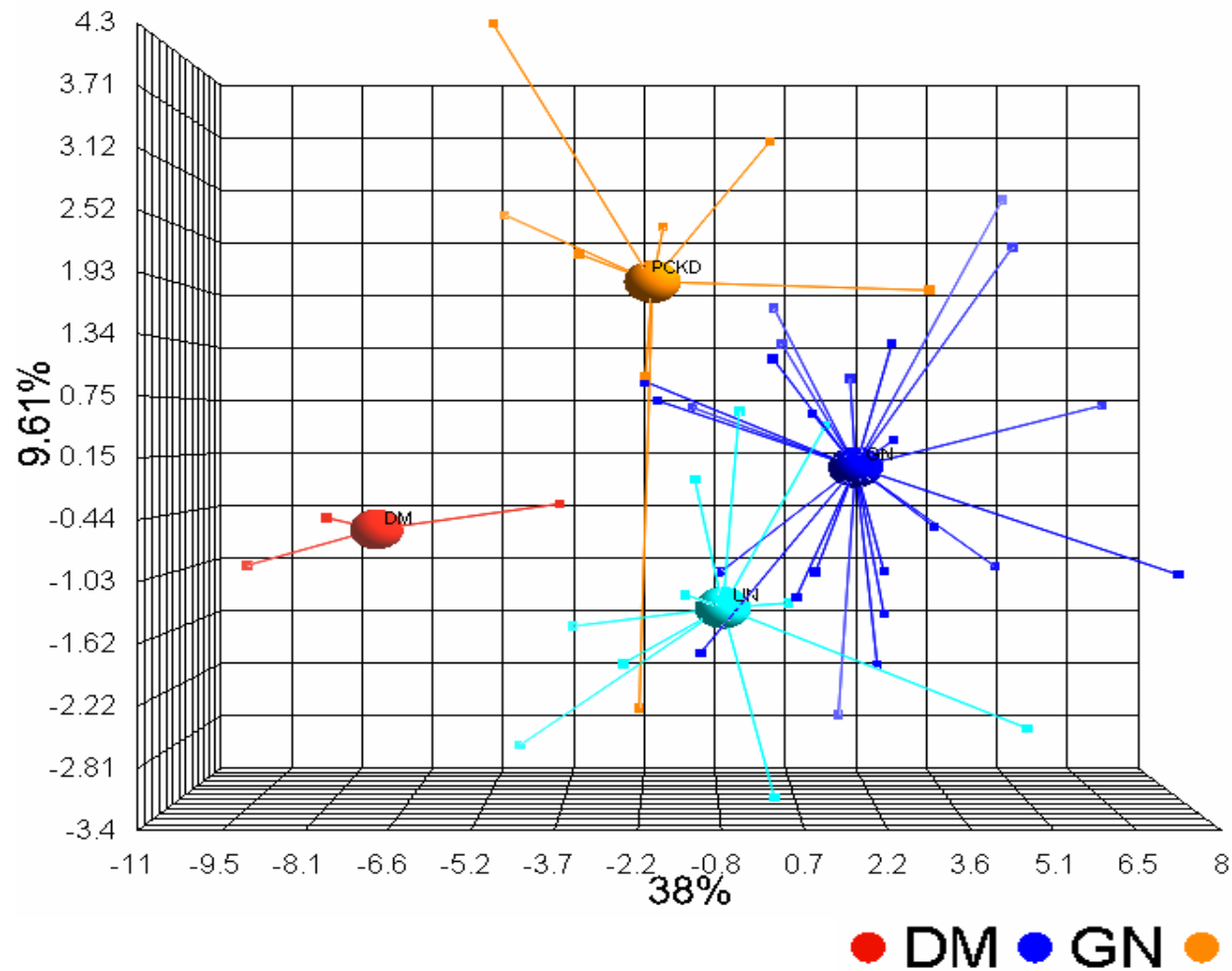
547 probe sets,
FDR<0.01



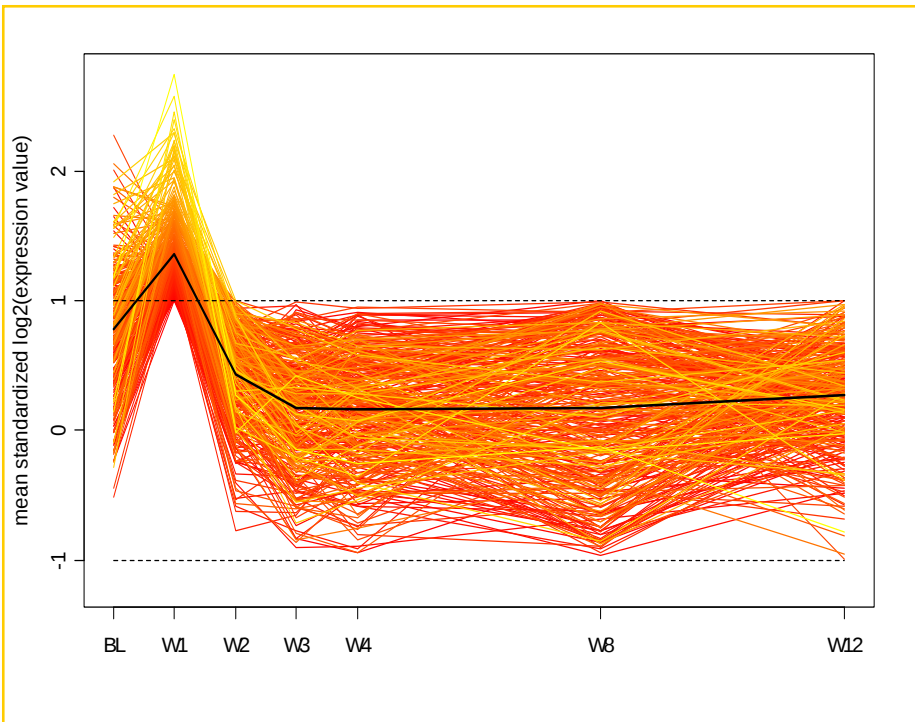
25 probe sets,
FDR<5x10⁻⁶



DIFFERENTIAL EXPRESSION BY PRIMARY DISEASE



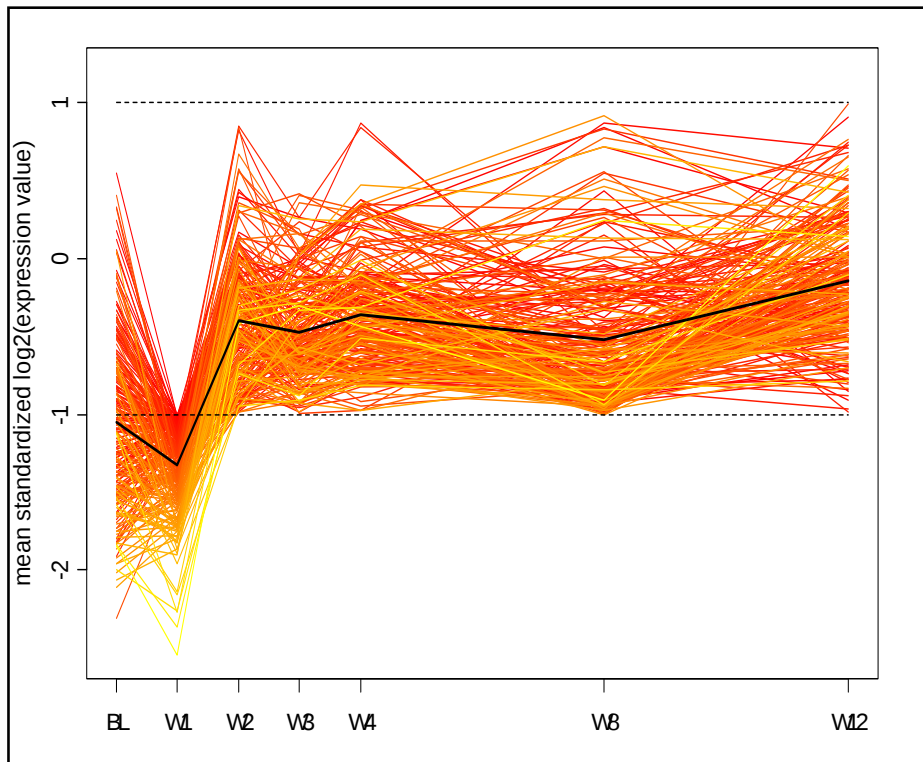
Differential expression



GO higher level categories

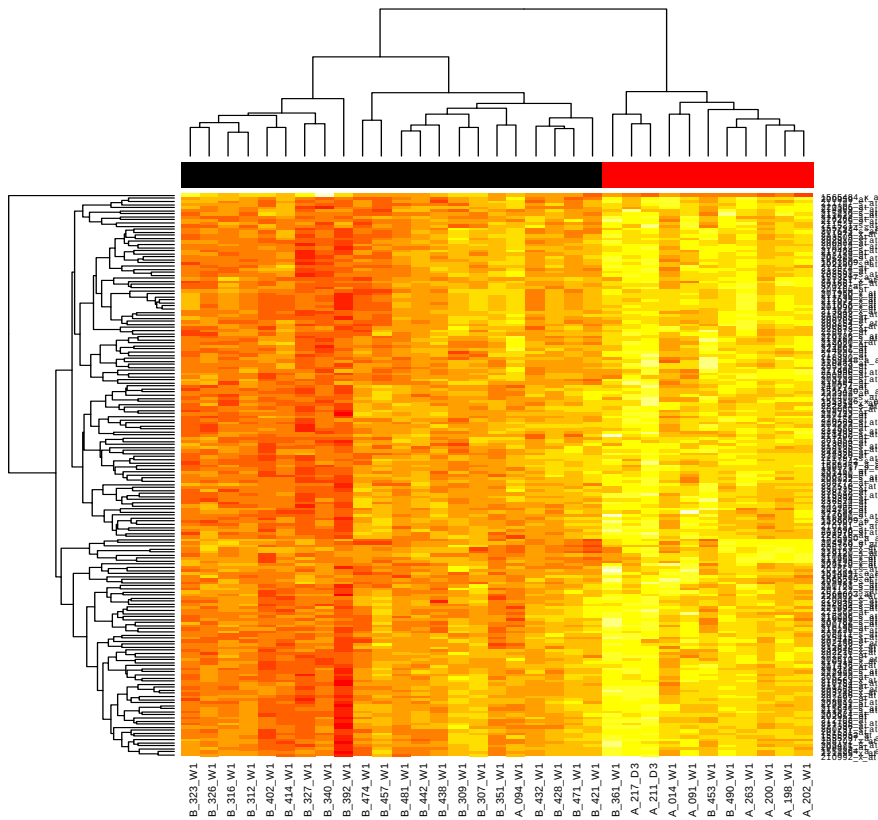
1. Chemotaxis and cell migration
2. Inflammation and innate immunity
3. Adaptive immunity (T- and B-cell)
4. Wounding and tissue healing
5. Other biological, cellular processes

Differential expression

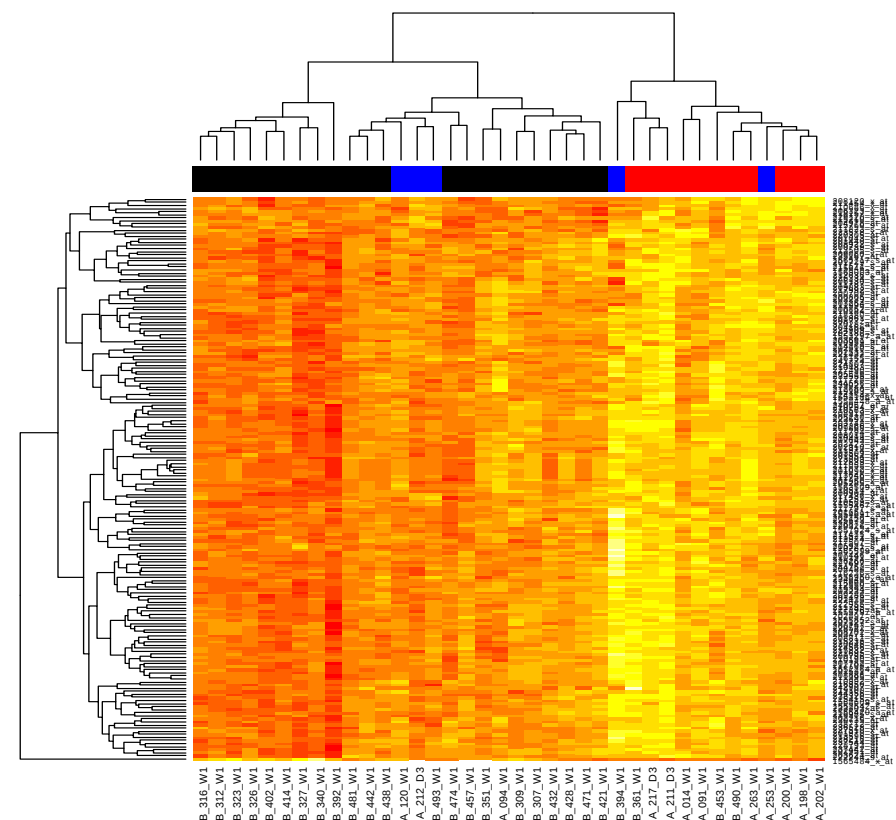


GO higher level categories

1. Defense response to infection
2. Embryonic growth and development
3. Innate immune response
4. Adaptive immunity
5. Other biological, cellular processes

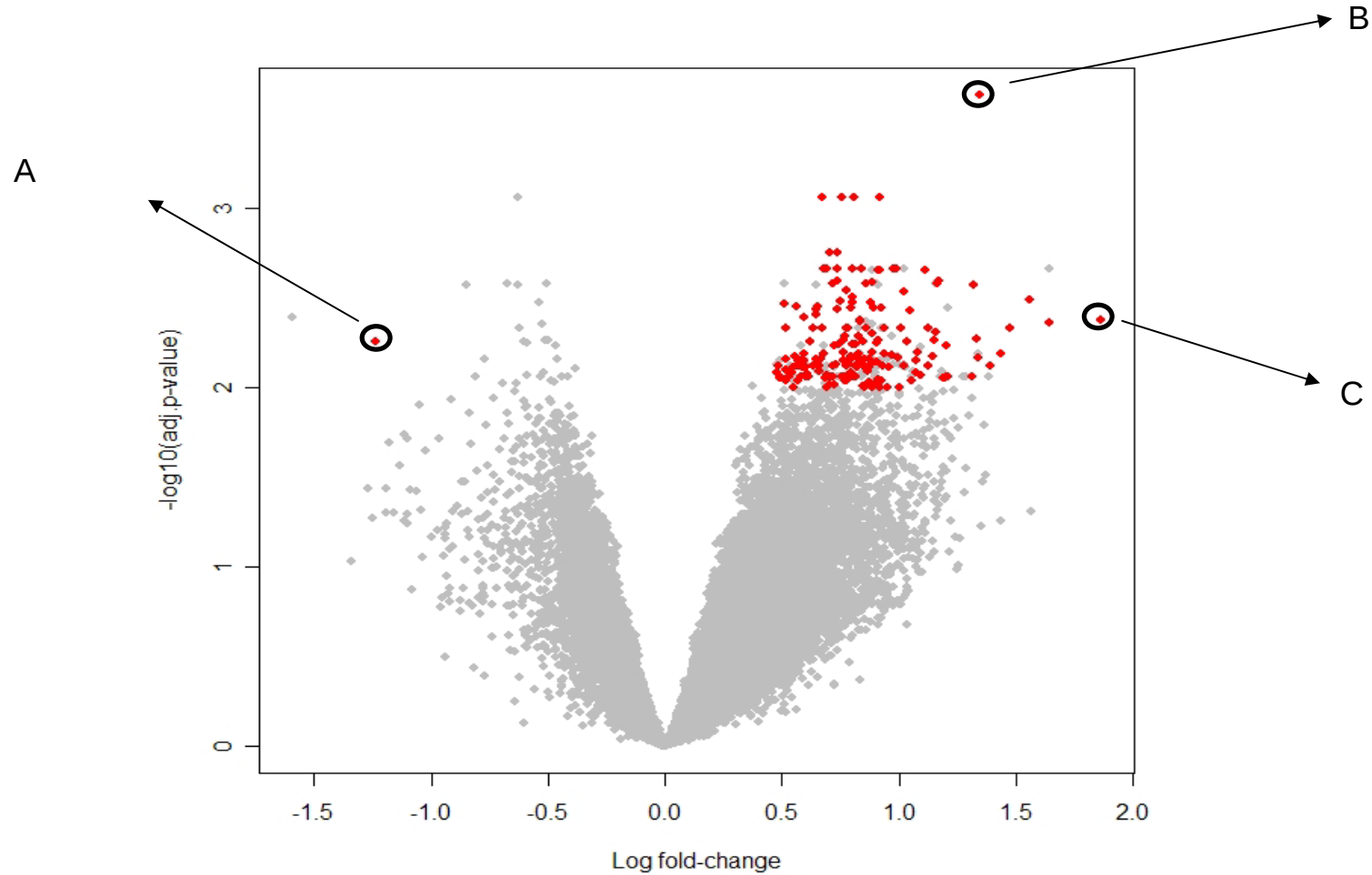


Acute Rejection



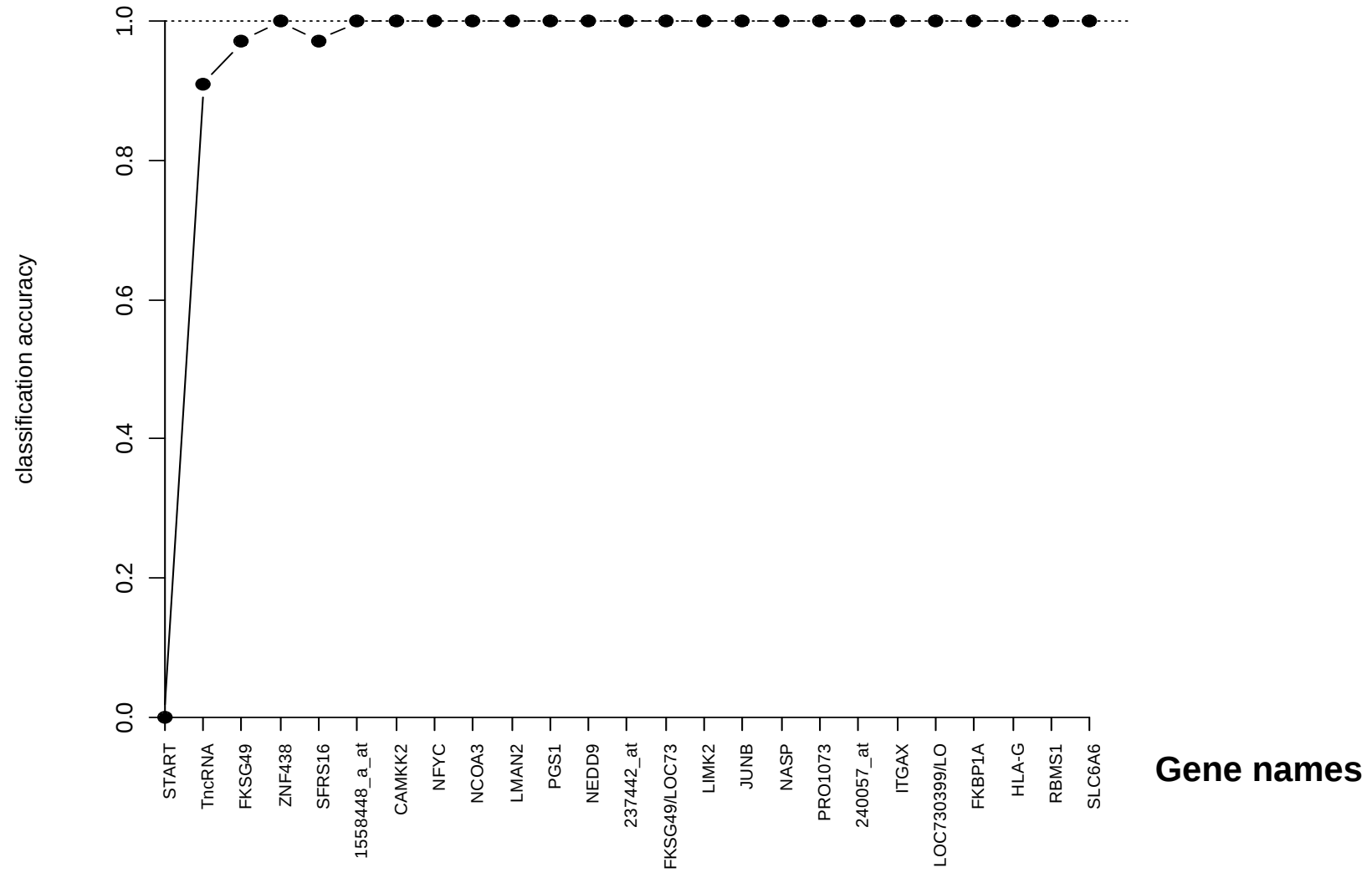
Borderline Rejection

No Rejection

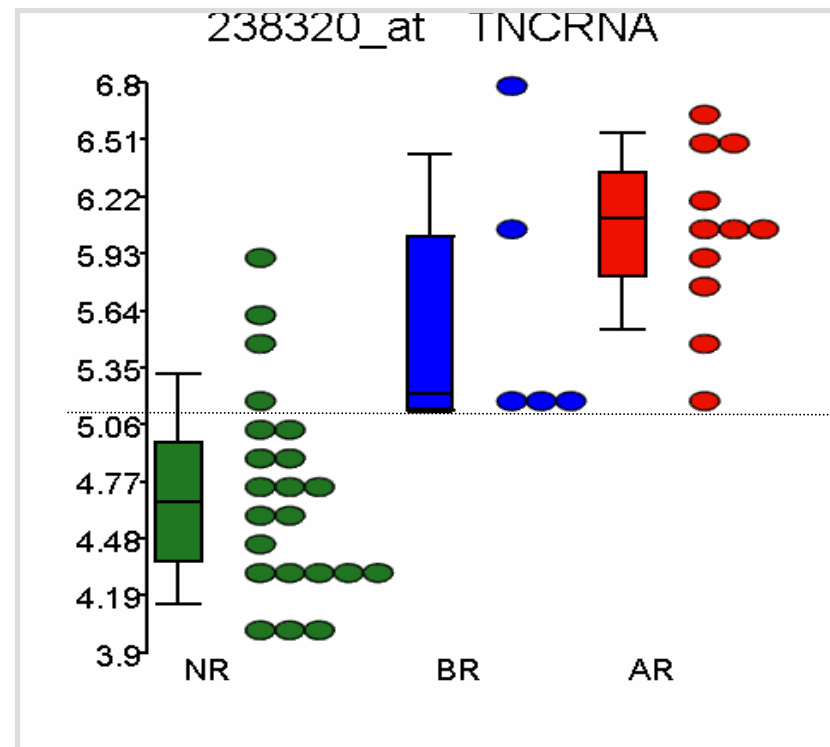


183 significant probe-sets (<1%; 3-method intersection)

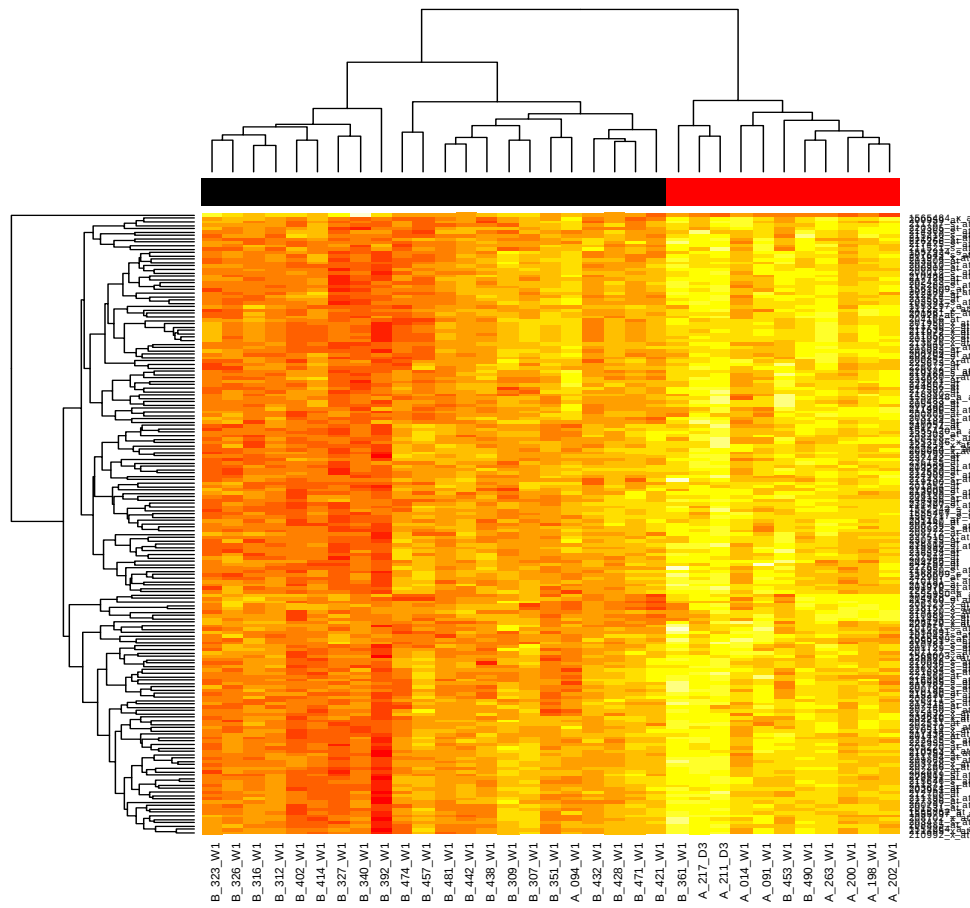
238320_at	TncRNA	trophoblast-derived noncoding RNA
211454_x_at	FKSG49	Protein of unknown function DUF741
244752_at	ZNF438	Zinc finger protein 438
204978_at	SFRS16	splicing factor, arginine/serine-rich 16
1558448_a_at	CDNA FLJ35687 fis	-
210787_s_at	CAMKK2	calcium/calmodulin-dependent protein kinase kinase 2, beta
211251_x_at	NFYC	nuclear transcription factor Y, gamma
209060_x_at	NCOA3	nuclear receptor coactivator 3
200805_at	LMAN2	lectin, mannose-binding 2
226266_at	PGS1	phosphatidylglycerophosphate synthase 1
202150_s_at	NEDD9	neural precursor cell expressed, developmentally down-regulated 9
237442_at	CDNA FLJ35687 fis	-
208129.x_at	FKSG49L.0C73	-
217475_s_at	LIMK	LIM domain kinase 2
201473_at	JUNB	jun B proto-oncogene
201970_s_at	NASP	nuclear autoantigenic sperm protein (histone-binding)
227510_x_at	PRO1073	CCNL1 (cyclin L1) ?
240057_at	CDNA FLJ35687 fis	-
210184_at	ITGAX	integrin, alpha X (complement component 3 receptor 4 subunit)
217436_x_at	LOC730399/LOC731974	hypothetical protein Human MHC class I HLA-J gene, exons 1-8
200709_at	FKBP1A	FK506 binding protein 1A, 12kDa
210514_x_at	HLA-G	HLA-G histocompatibility antigen, class I, G
203748_x_at	RBMS1	RNA binding motif, single stranded interacting protein 1
205921_s_at	SLC6A6	solute carrier family 6 (neurotransmitter transporter, taurine), member 6



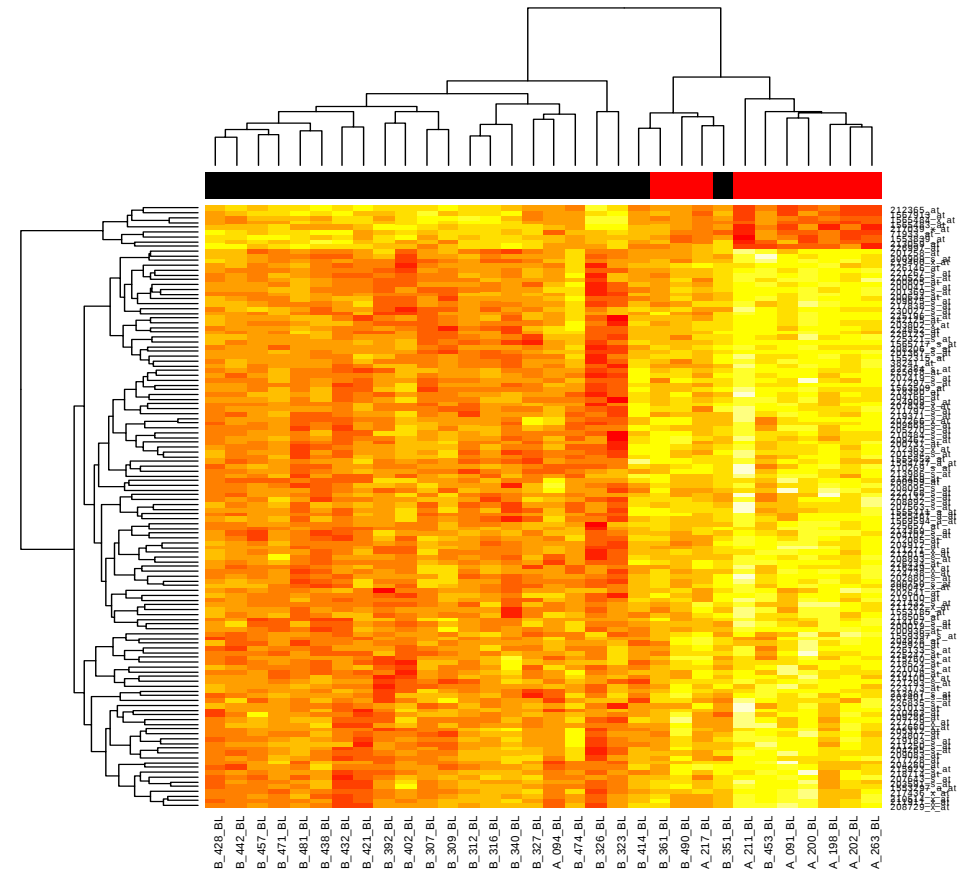
1 probe set of 17338 with 78% correct classification rate



	# Per Class	Proportion	# Correct	# Errors	% Correct
BR	5	0.13	3	2	60.00
NR	22	0.58	18	4	82.00
AR	11	0.29	9	2	82.00
The Average					74.67
Total	38	1	30	8	78.95

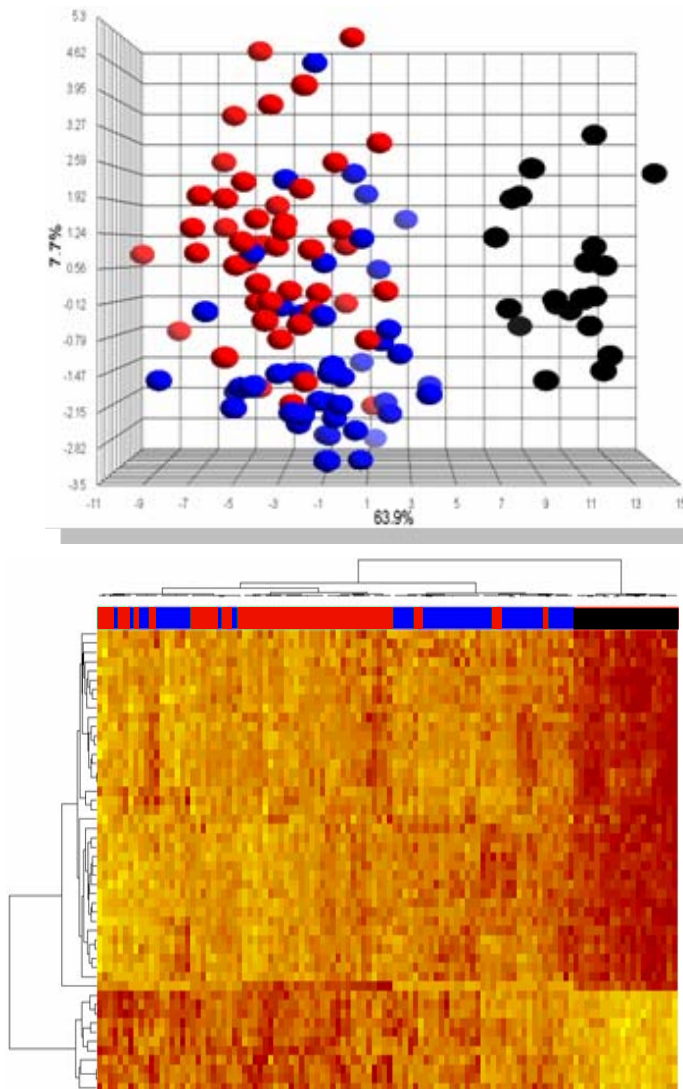


**183 significant probe sets AR
vs NR at W1**



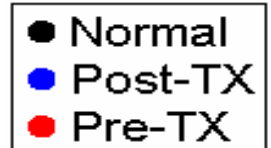
**126 significant probe sets
AR vs NR pre-transplant**

GENE SIGNATURES IN METASTABLE TRANSPLANTS

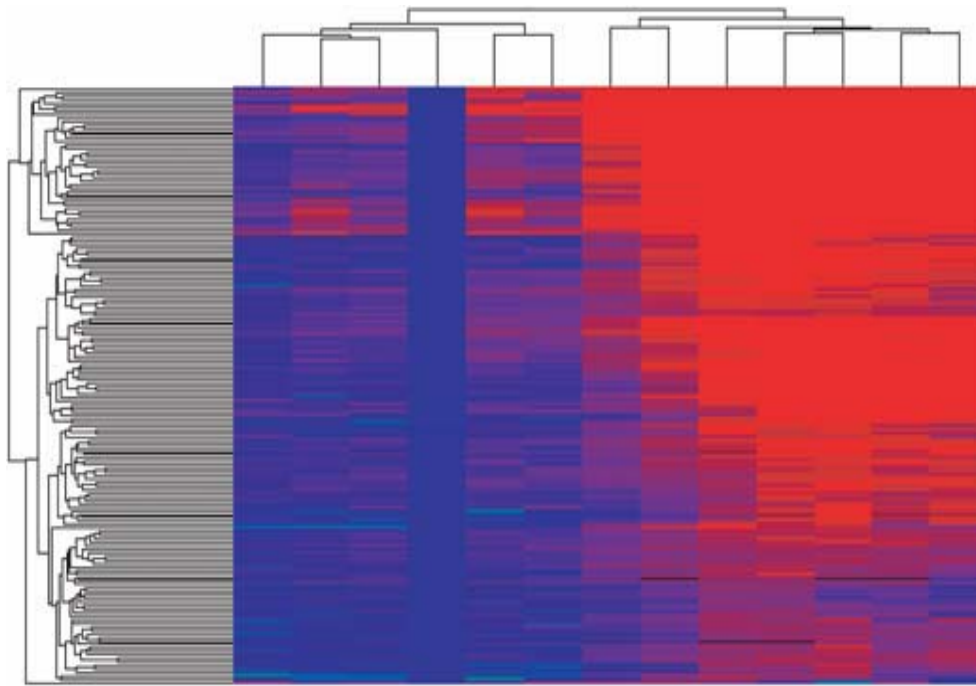


Gene categories altered

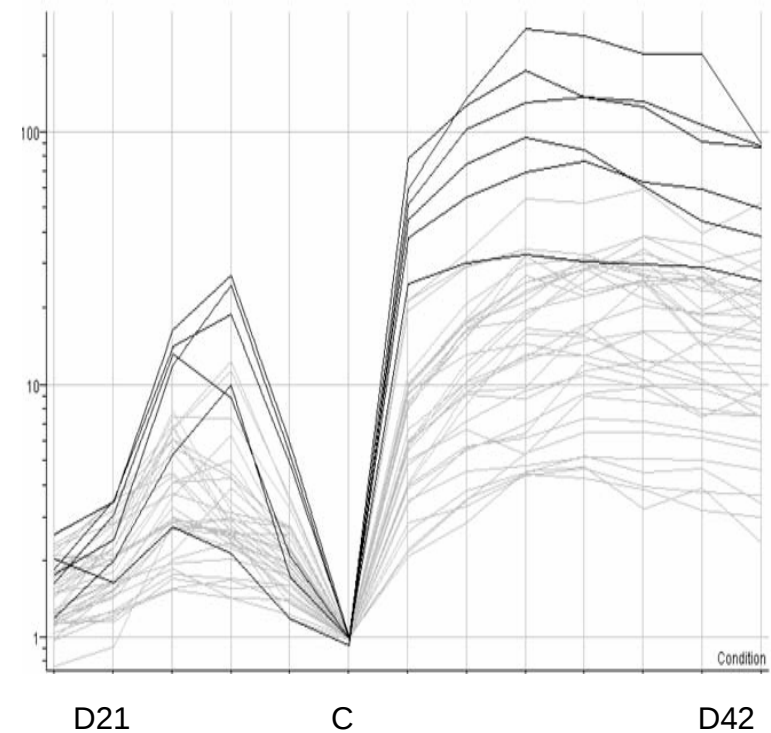
1. Energy and transport regulation
2. Immune defense and antibodies
3. Nuclear transport and signaling
4. Control of intermediary metabolism
5. Other biological, cellular processes



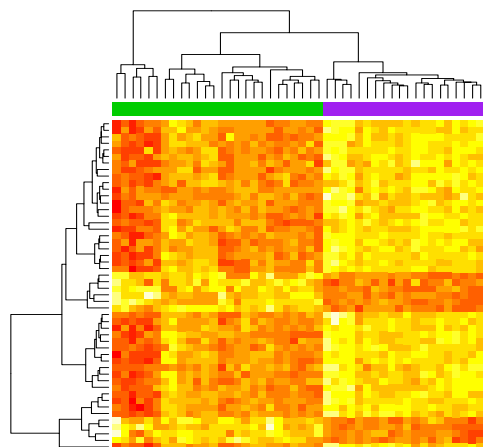
GENE SIGNATURES IN MURINE KIDNEY POST TRANSPLANT



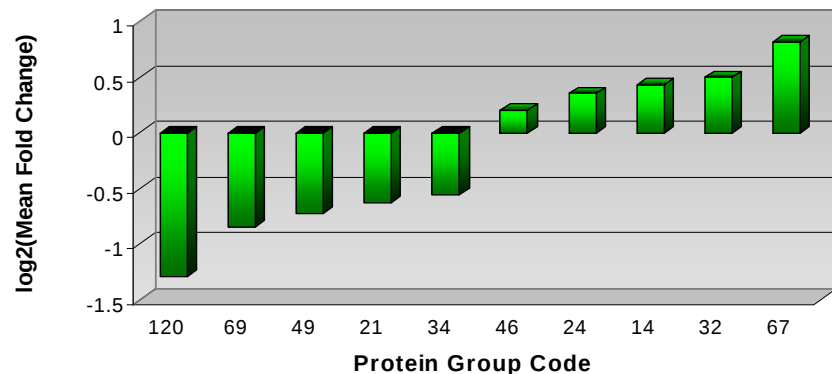
BC023105
Ccl5
Ccl8
Cxcl11
Ifi202b
Vcam1
Dnase1l3
Casp7
Parp3
Stat2
Tcf7
Trim21
Trim34
Card4
Ccl19
Ccr9
Il18
Parp11



Endstage Heart Failure

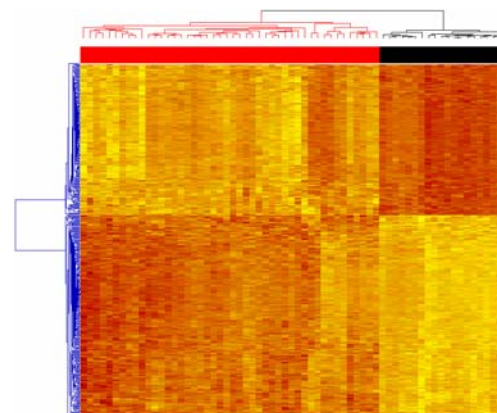
G
E
N
O
M
I
C
S

7,368 probe sets were significantly differentially expressed in **heart failure** versus normal

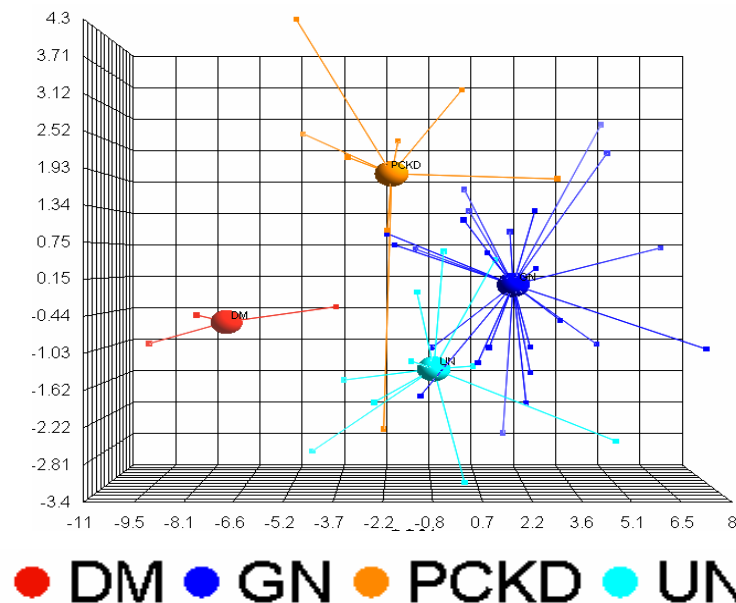
P
R
O
T
E
O
M
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S

45 protein groups were significantly differentially expressed in heart failure versus normal

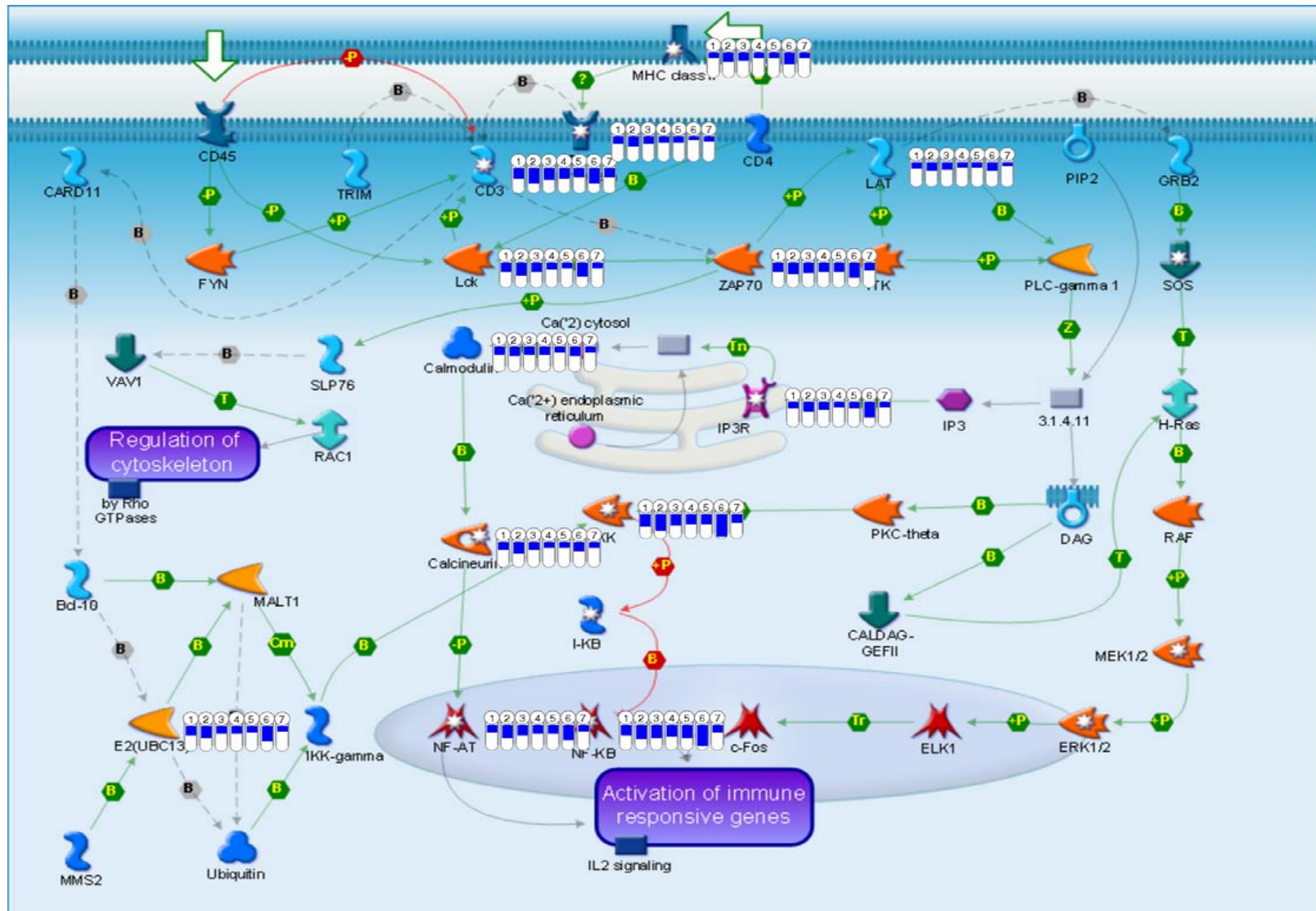
Endstage Kidney Failure



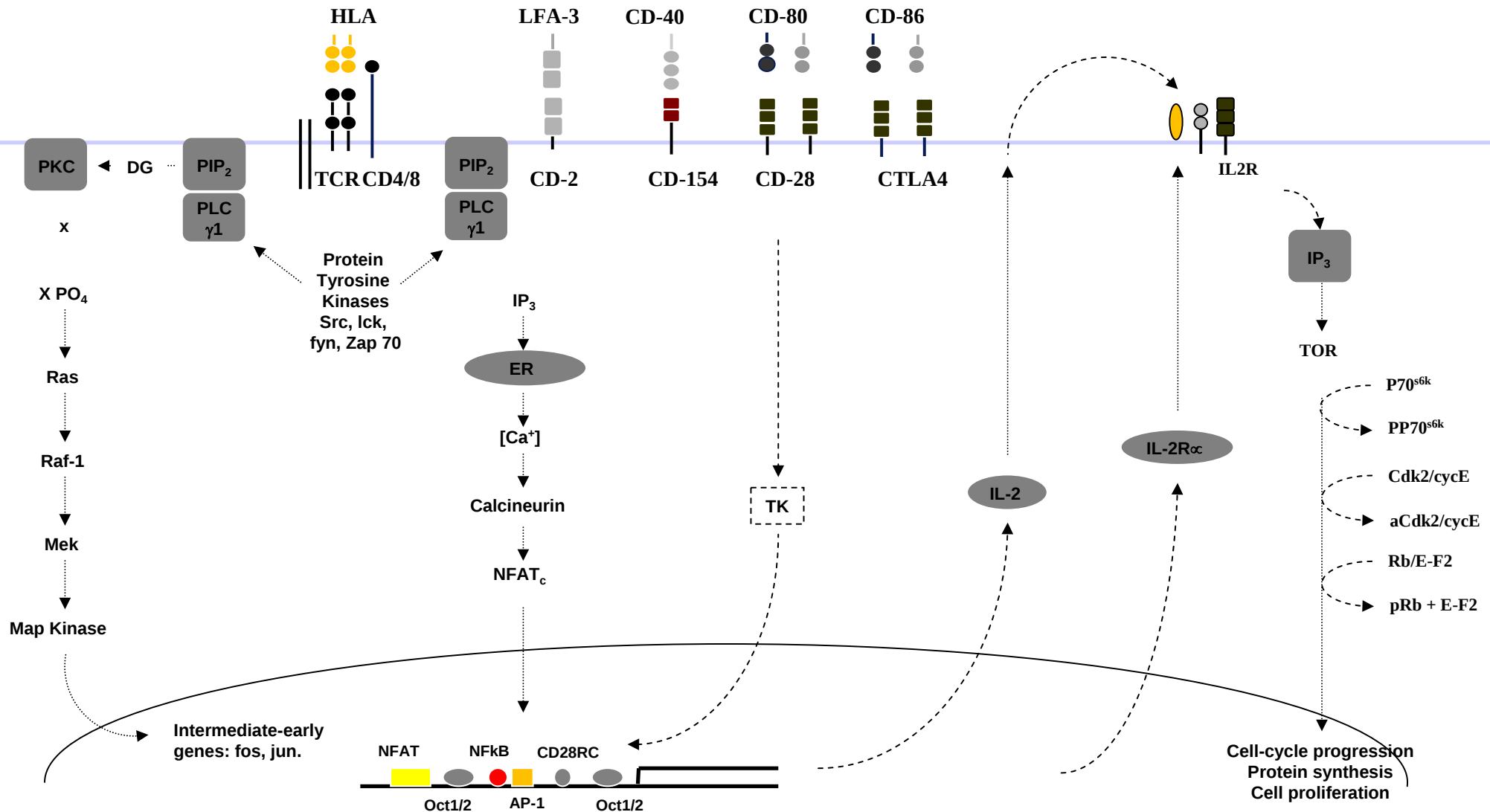
10,484 probe sets were significantly differentially expressed in **kidney failure** versus normal



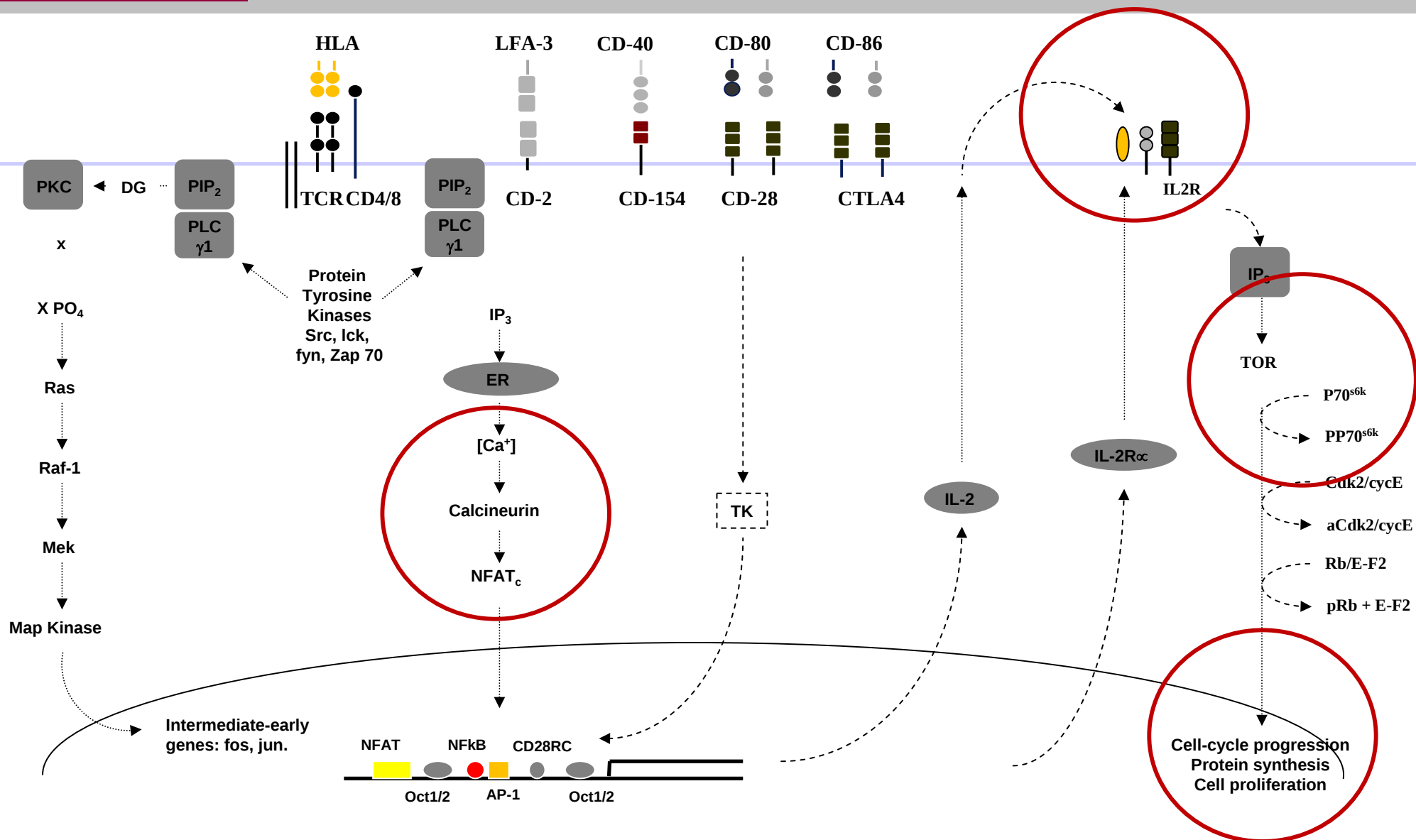
PATHWAY ANALYSIS IN RENAL TRANSPLANTATION



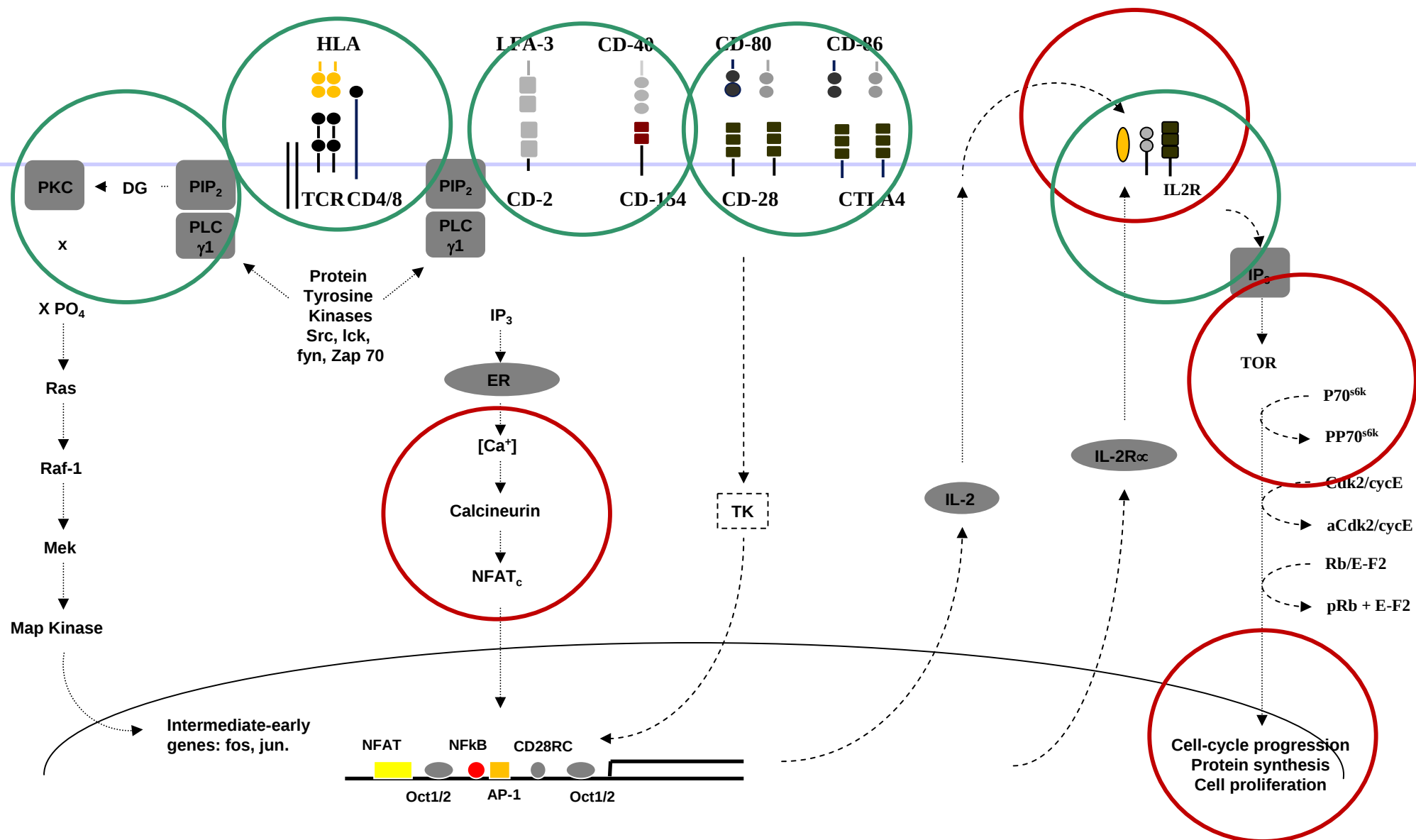
MOLECULAR ACTIVATION OF THE T-CELL

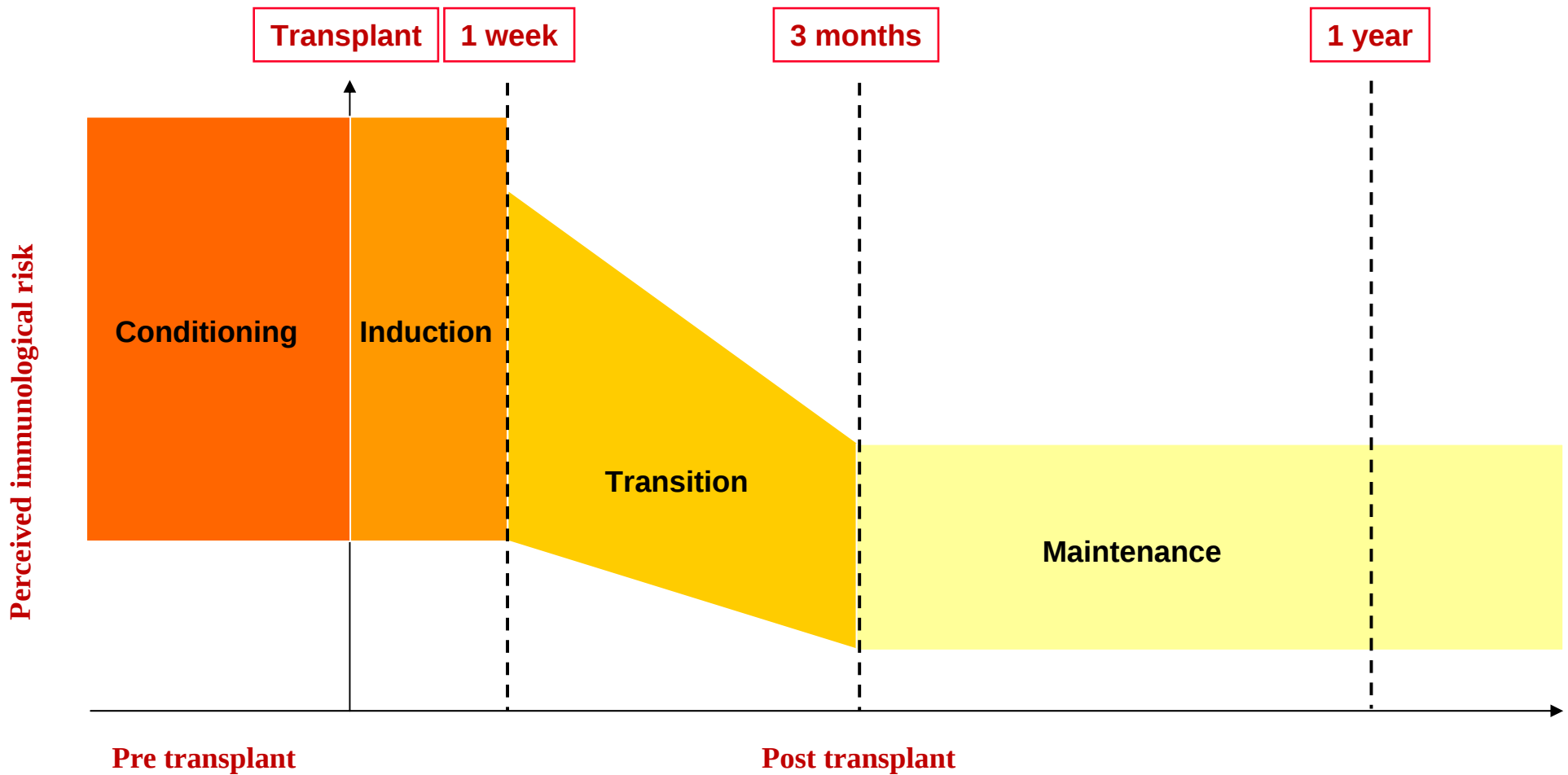


MOLECULAR ACTION OF CURRENT IMMUNE SUPPRESSANTS



MOLECULAR ACTION OF NOVEL IMMUNE SUPPRESSANTS





- **Confirmation** – validation of the initial discoveries in a multi-centre Canadian study
- **Application** – development of simple and rapid biomarkers using routine laboratory methods
- **Exploration** – understanding of the mechanisms controlling accommodation and tolerance
- **Translation** – use of these discoveries to develop new drugs and treatment to improve graft outcome



The GENOME Team



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Funding Partners

Genome Canada, Novartis, IBM, Genome BC, Other Partners