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Allgemein öffentliches Krankenhaus
Elisabethinen Linz

Genomics, Proteomics,Transcriptomics – a Systems Biology Approach to CKD

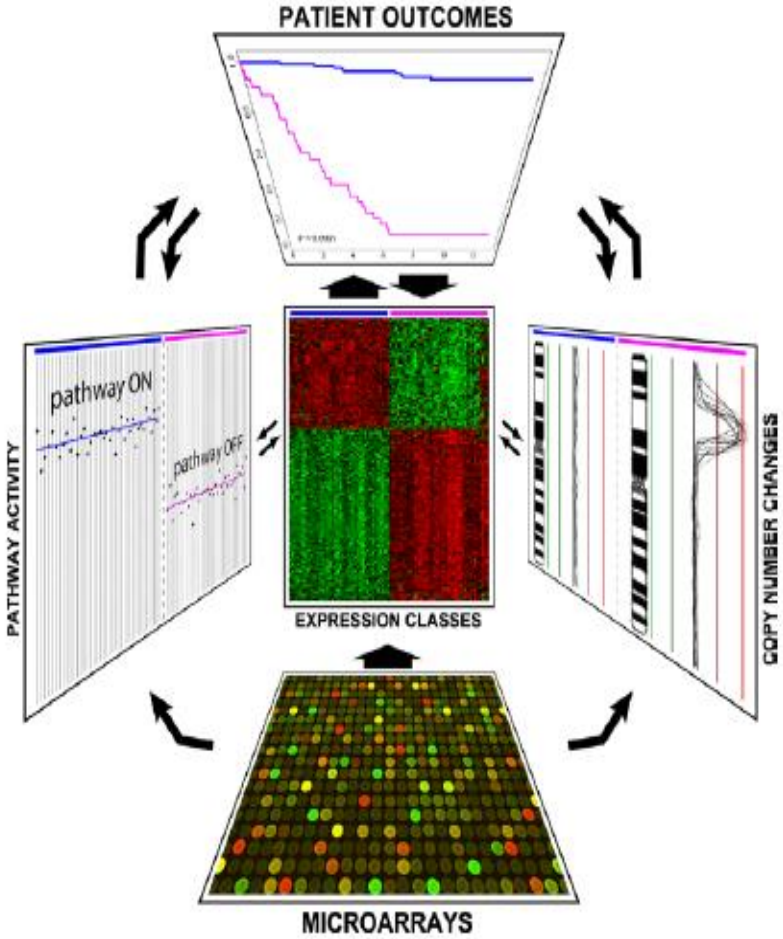
Rainer Oberbauer

What is ‚Omics‘?

- Neologism ‘omics’ informally refers to a field of study ending in -omics, such as genomics or proteomics.

- All constituents considered collectively

What is Systems Biology?



Perco P, Electrophoresis 2006; 27(13):2659-2675.

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Genomics

order now

news

core values

policy forum

corporate info

jobs

Who We Are

Board of Directors

Editorial Team

Advisors

Team 23andMe

about us

Mission Statement

23andMe's mission is to be the world's trusted source of personal genetic information.

A Snapshot of Team 23andMe

previous

next

67% of us have a family history of cancer

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https://www.23andme.com/

genetic epidemiology - Googl... | MUW-Webmail | 23andMe - Genetics Just ...

23andMe genetics just got personal.

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1866: Gregor Mendel discovers the laws of inheritan

200,000 years ago: *Homo sapiens* walks the Earth.

2003: The Human Genom

2007: 23andMe introduces the first Personal (

Unlock the secrets of your own DNA.

Welcome to 23andMe, a web-based service that helps you read and understand your DNA. After providing a saliva sample using an at-home kit, you can use our interactive tools to shed new light on your distant ancestors, your close family and most of all, yourself.

Sign up for our Email Newsletter

news **What's new at 23andMe**

Mar 25, 2008: 23andMe introduces a new Ancestry Painting feature, enhances sharing and search features, and adds more Gene Journal content.

Gene Journal

What do your genes say about you?

Ancestry

Who were your ancient ancestors?

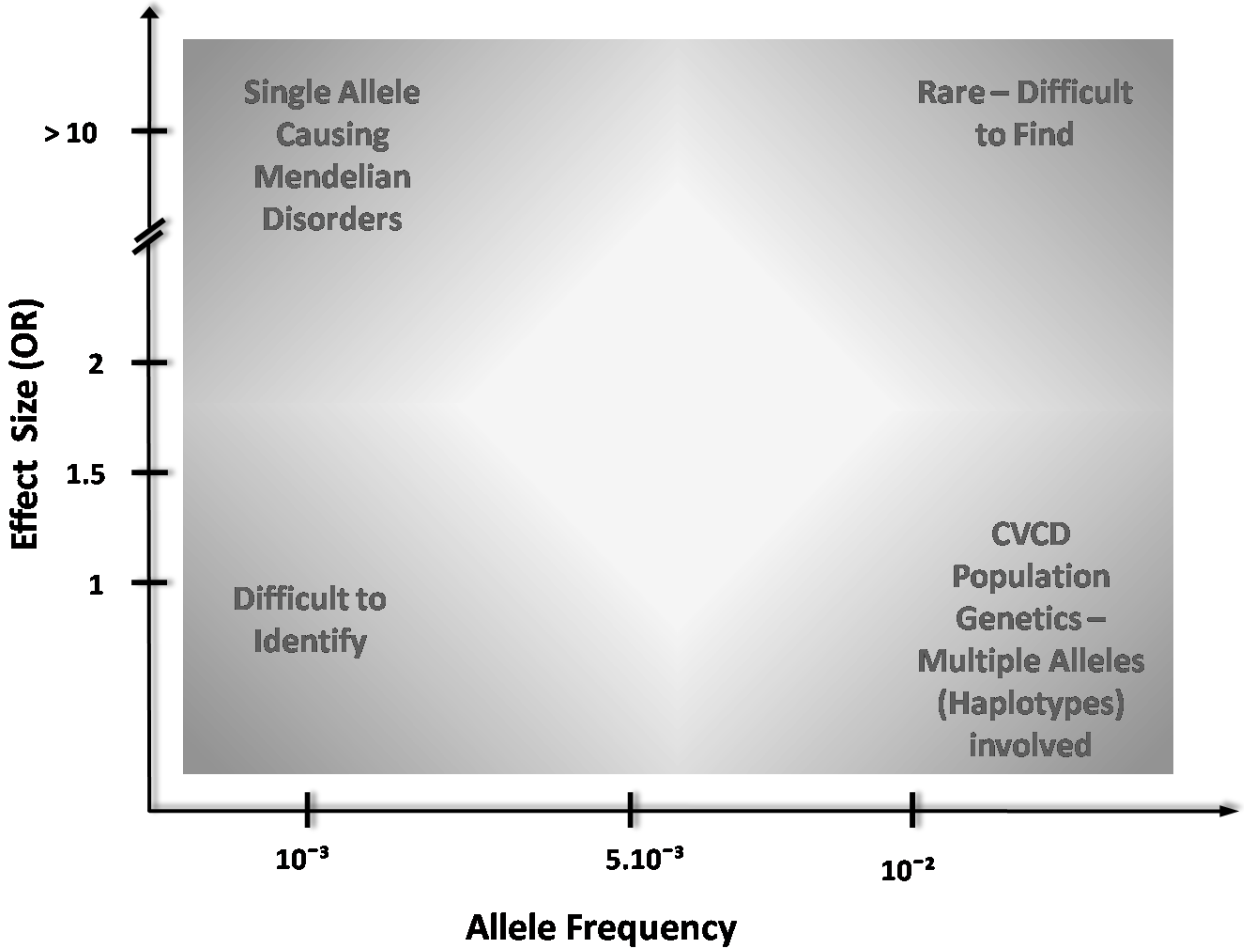
Family Inheritance

Do you have your mother's sense of taste?

Genome Labs

Would you like to search your genome?

Allele frequencies and effect sizes of genetic variants in human diseases - GWAS



Le, Y, Shiffman D, Oberbauer R. MMB 2010 (in press)

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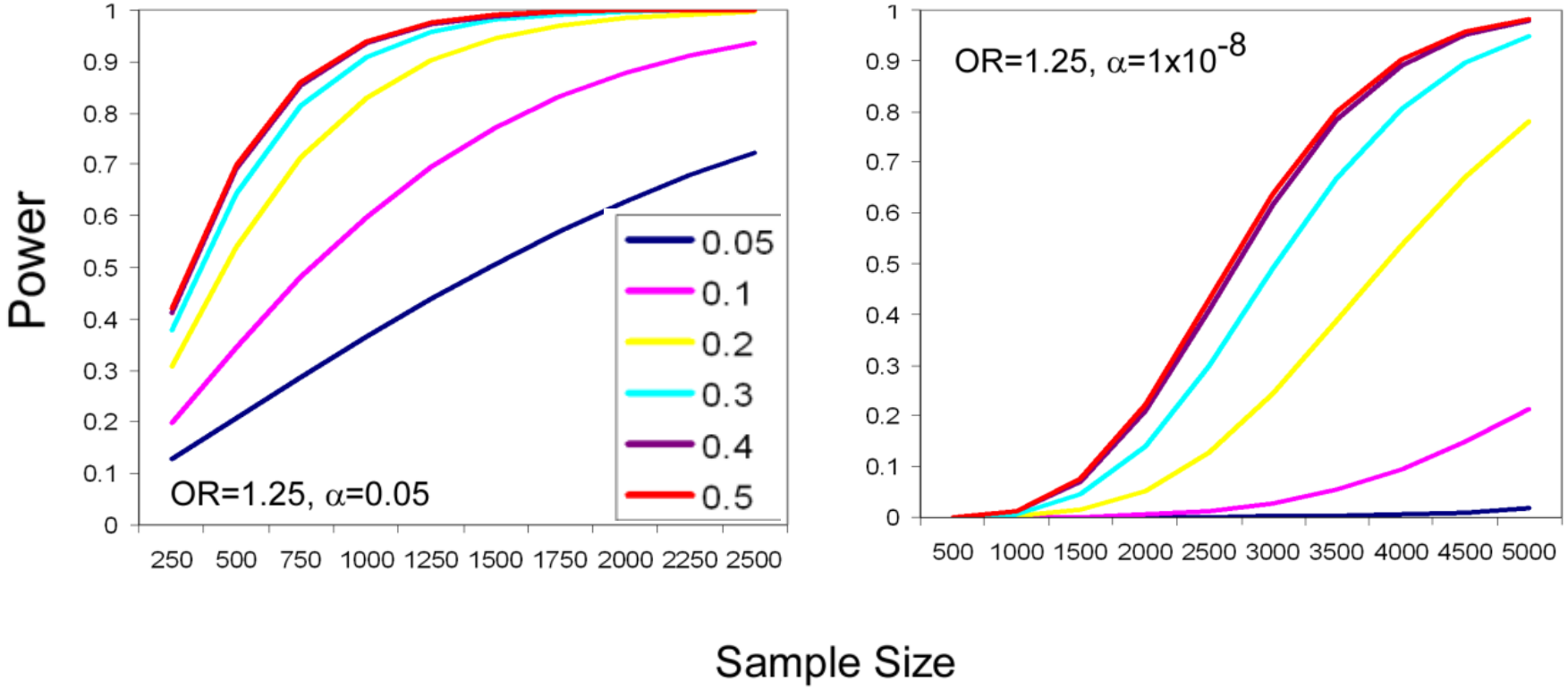
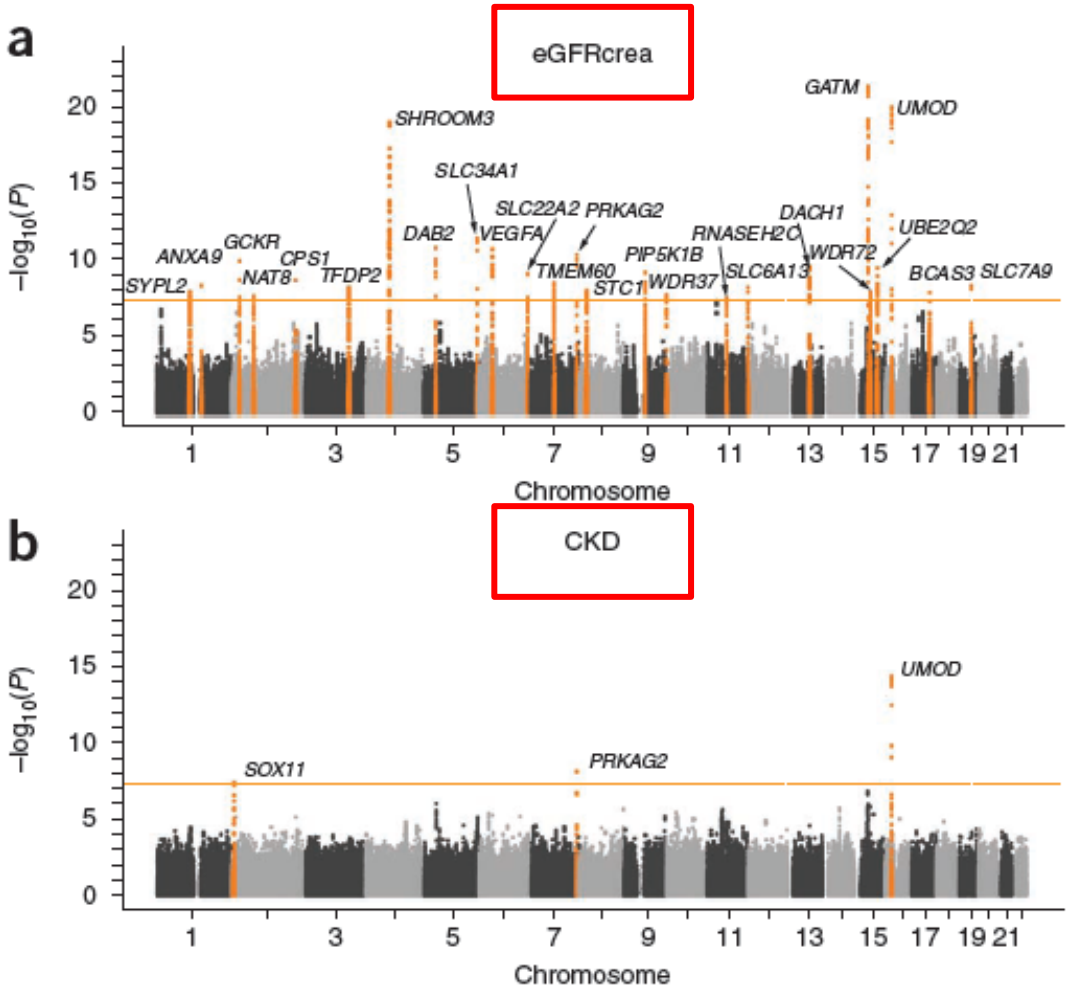
Sample size/power in GWAS



Le, Y, Shiffman D, Oberbauer R. MMB 2010 (in press)

GWAS and CKD



Kottgen A et al. Nat Genet. 2010 May;42(5):376-84

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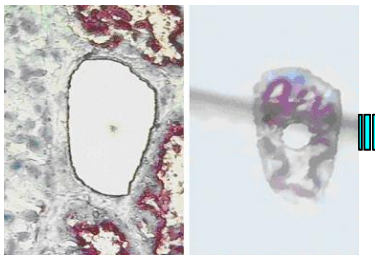
Systems biology of kidney injury

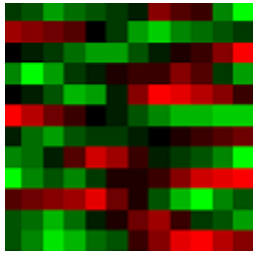
Laser Capture
Microdissection
Of Donor Kidneys

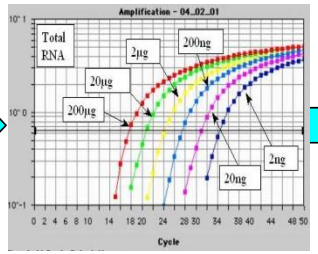
DNA
Microarrays

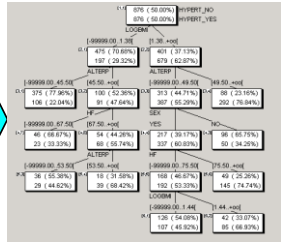
Quantitative
PCR

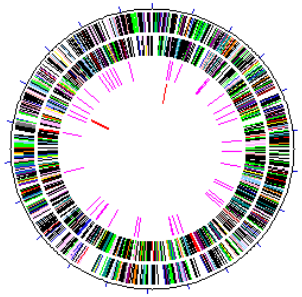
Data
Mining

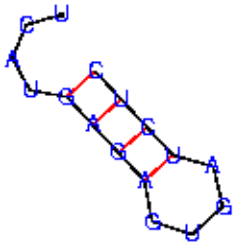


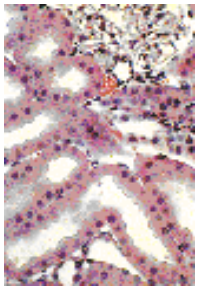


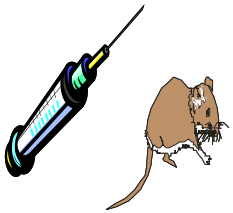












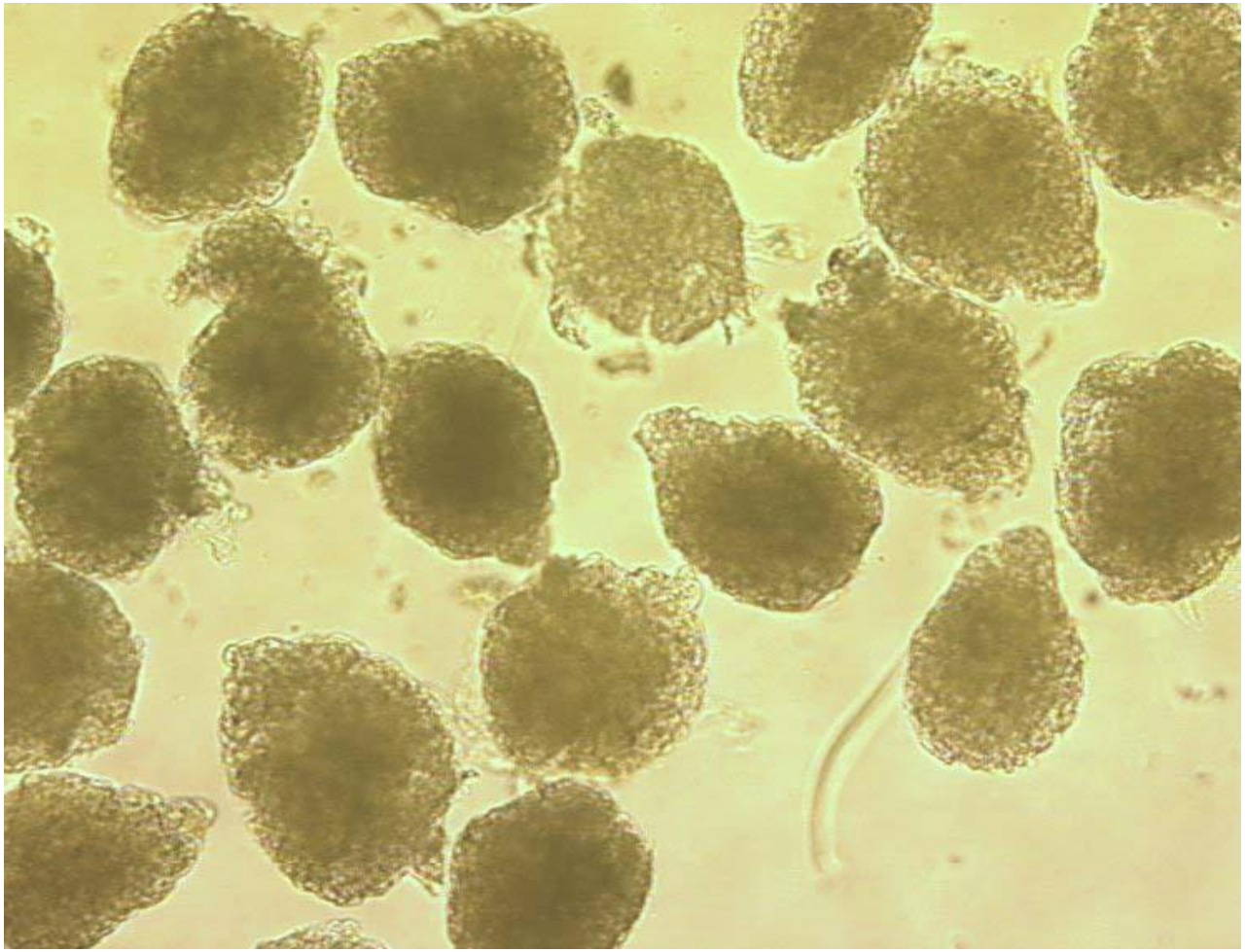
Target Gen
Definition

Antisense
Nucleotide
Design &
Synthese

In vitro
POC

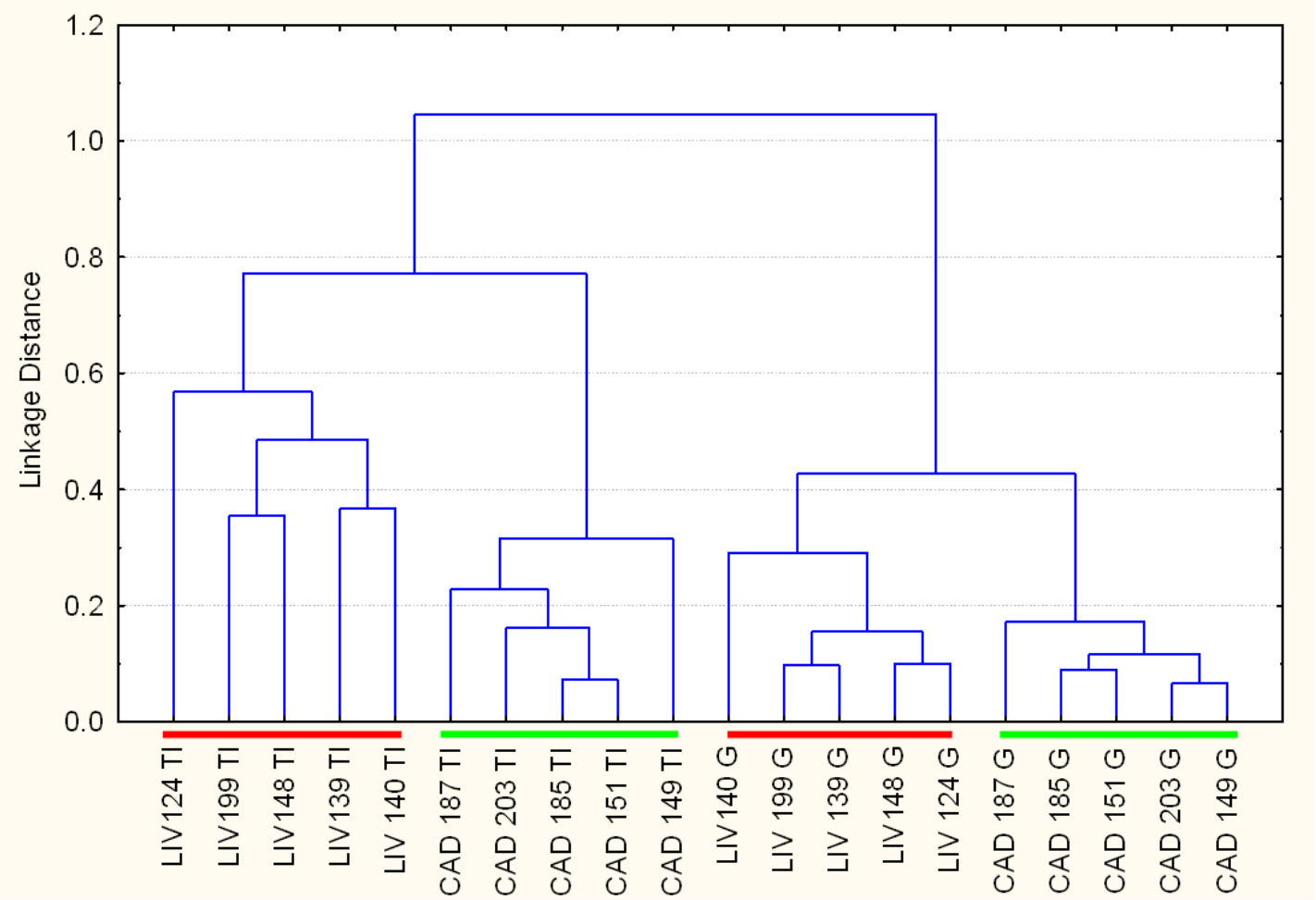
In vivo
POC

Glomeruli isolated from live and deceased donor kidney biopsies



Kainz A et al. *Am J Transplant* 2004; 4:1595-1604

Transcripts are specific for deceased and live donor kidney compartments



Kainz A et al. Am J Transplant 2004; 4:1595-1604

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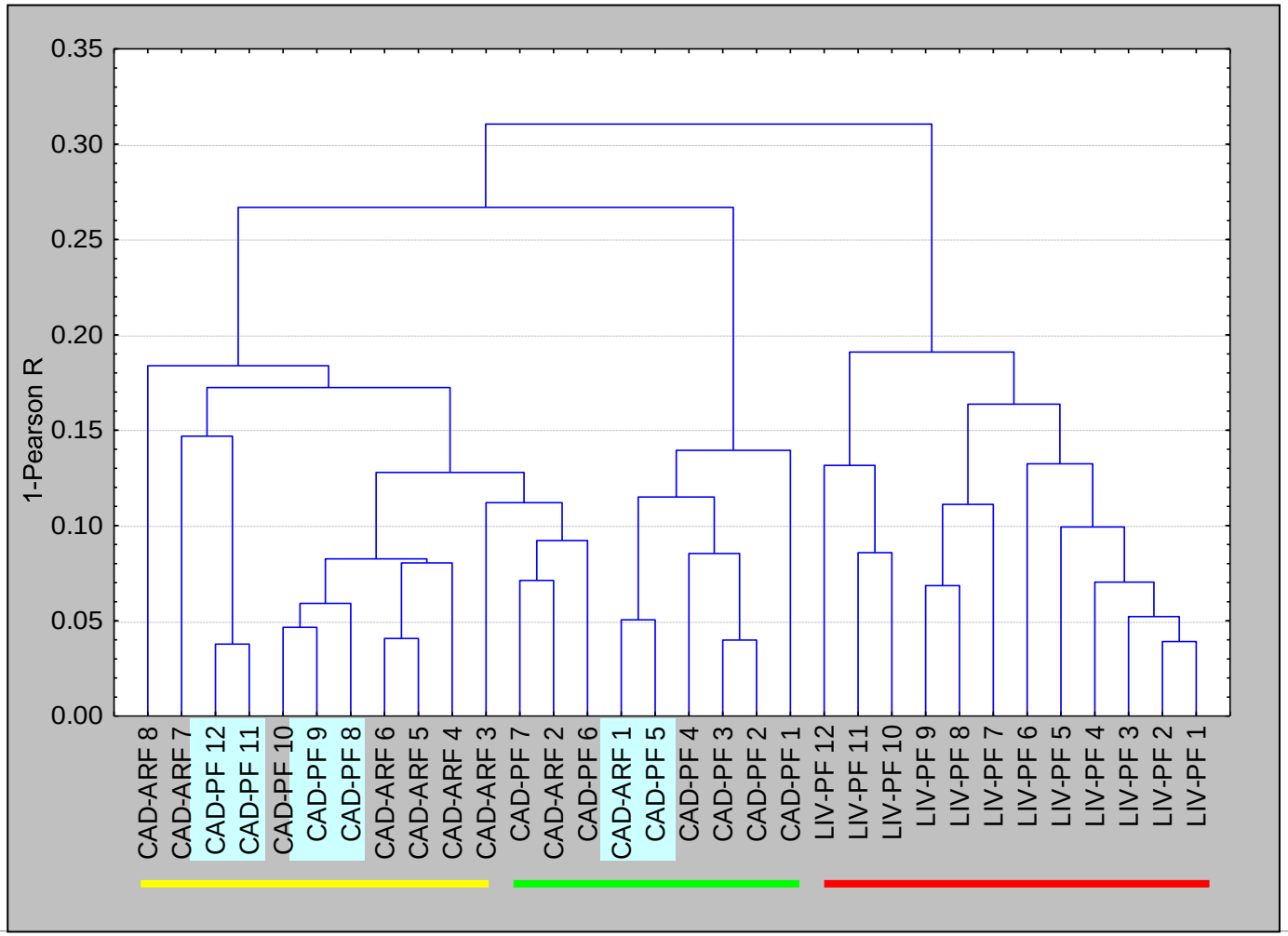
Unsupervised Cluster Analysis of Donor Kidney Biopsies



Hauser P et al, Lab Invest *2004, 84:353-61*

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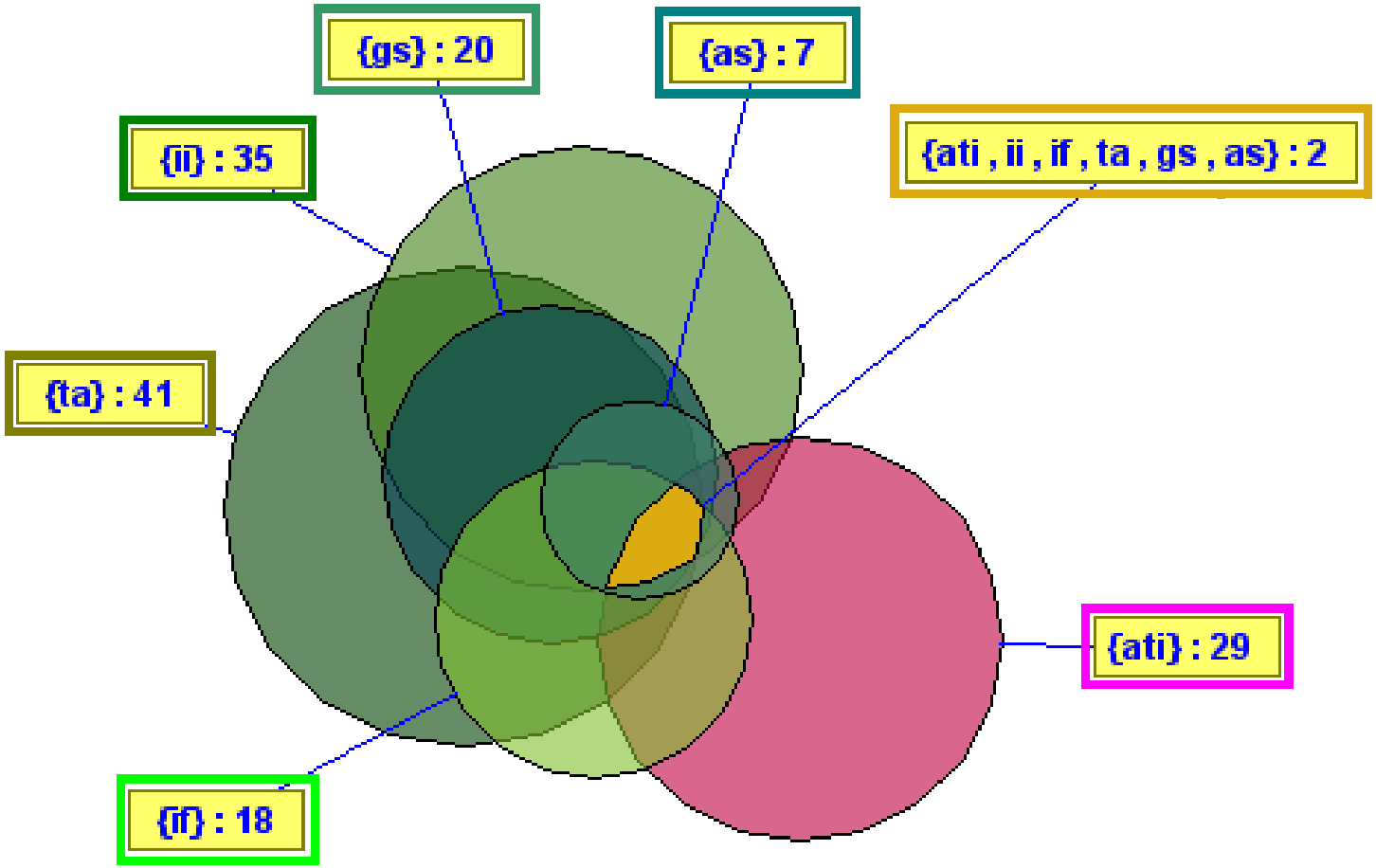
Histogenomics of deceased donor kidneys (n=82)



Perco P et al, *Transplantation. 2009 Jan 27;87(2):290-5.*

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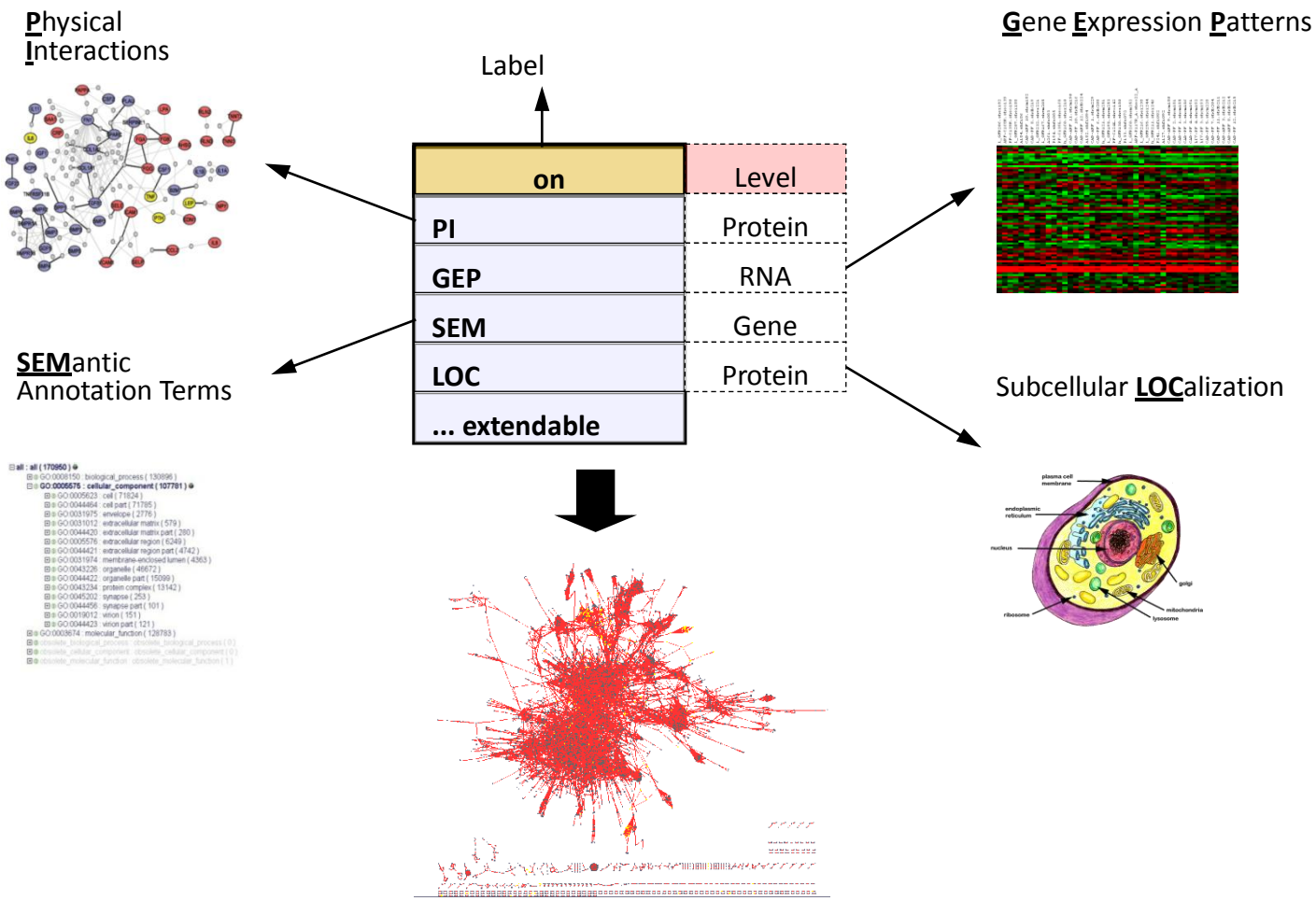
Systems Biology and omicsNET



Bernthaler A et al. 2009, *Mol Biosyst*, Jun 3 [ahead of print]

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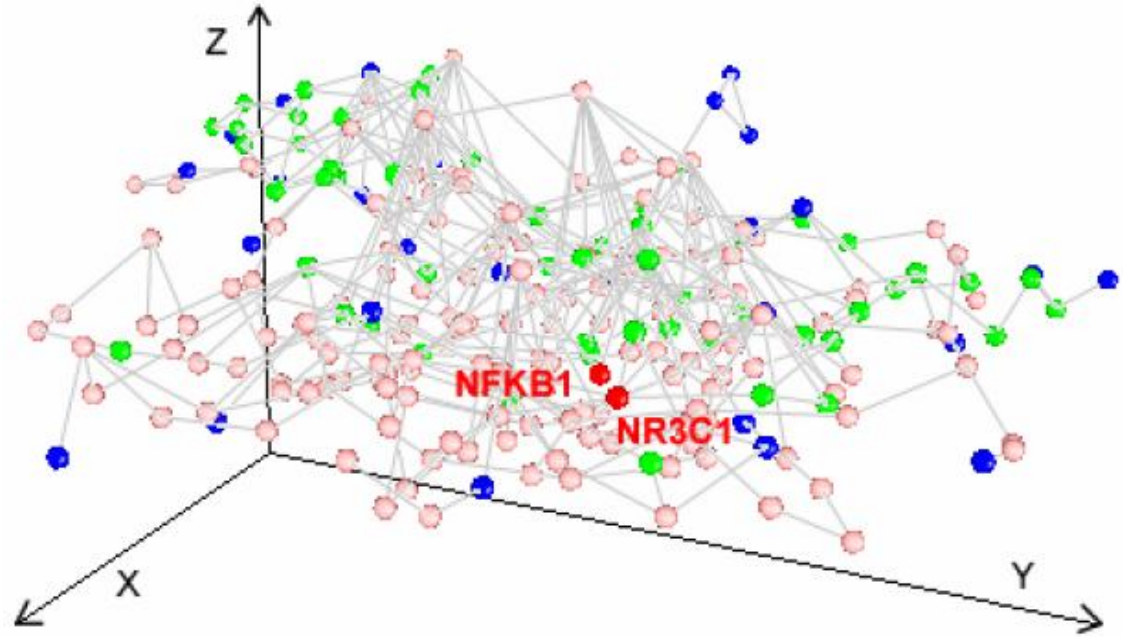
omicsNET – Example – IRI/ARF

Inflammation networks in cadaveric donor organs



Inflammation/immunity/defense

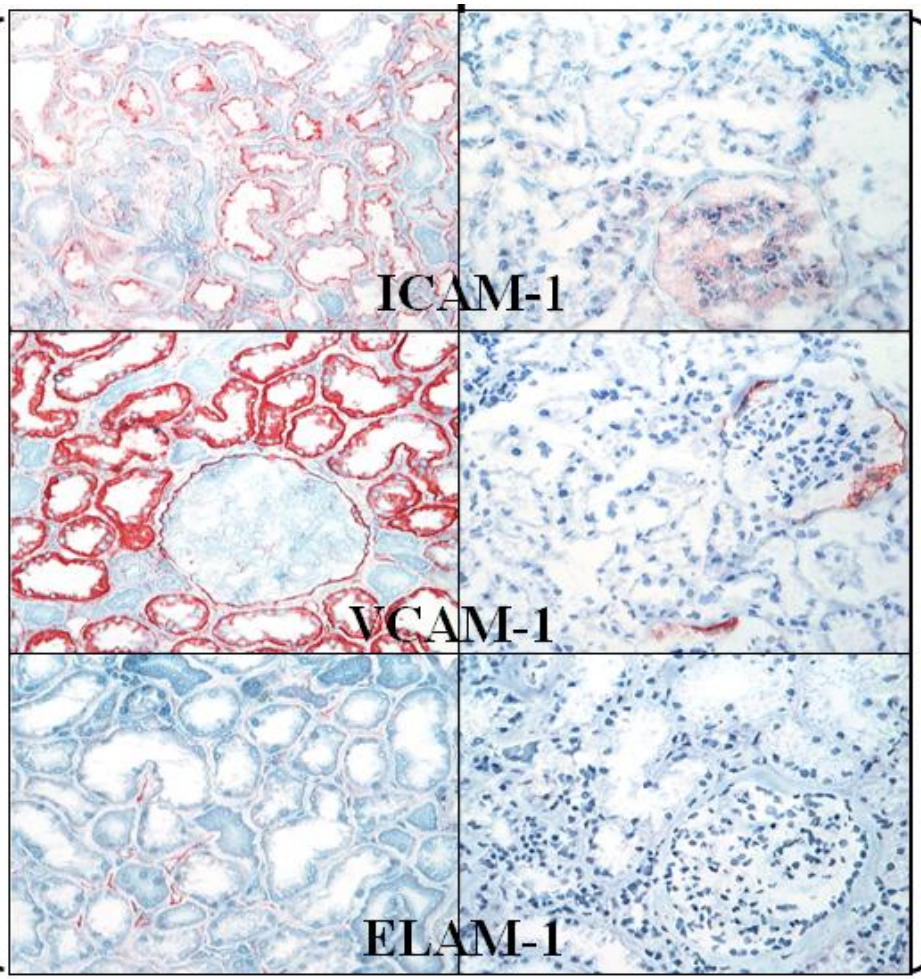
differentially regulated

cortisone targets

Mühlberger I et al. Transplantation 2009;88: 14–S19

Inflammation in Deceased Donor Kidney Biopsies

DGF



PGF

Schwarz et al Transplantation 2001:71:1666-72

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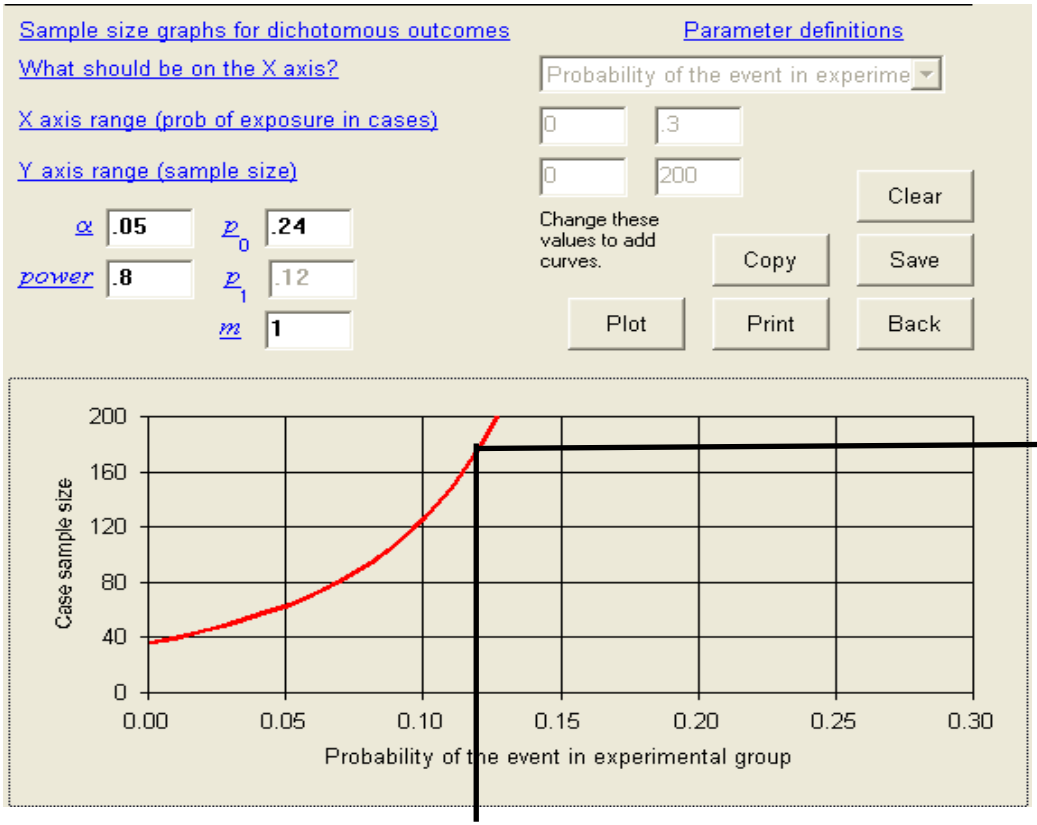
A Multicenter Double-Blinded RCT of Deceased Organ Donor Pre-Treatment with Corticosteroids for the Prevention of Postischemic Acute Renal Allograft Failure

Current Controlled Trials Registration #:
ISRCTN78828338

Sponsor: FWF P15679, €350k 3yrs

Kainz A et al. Ann Int Medicine 2010

Sample size estimation



12%

Event rate control group = 24%

Computed sample size to half event rate :

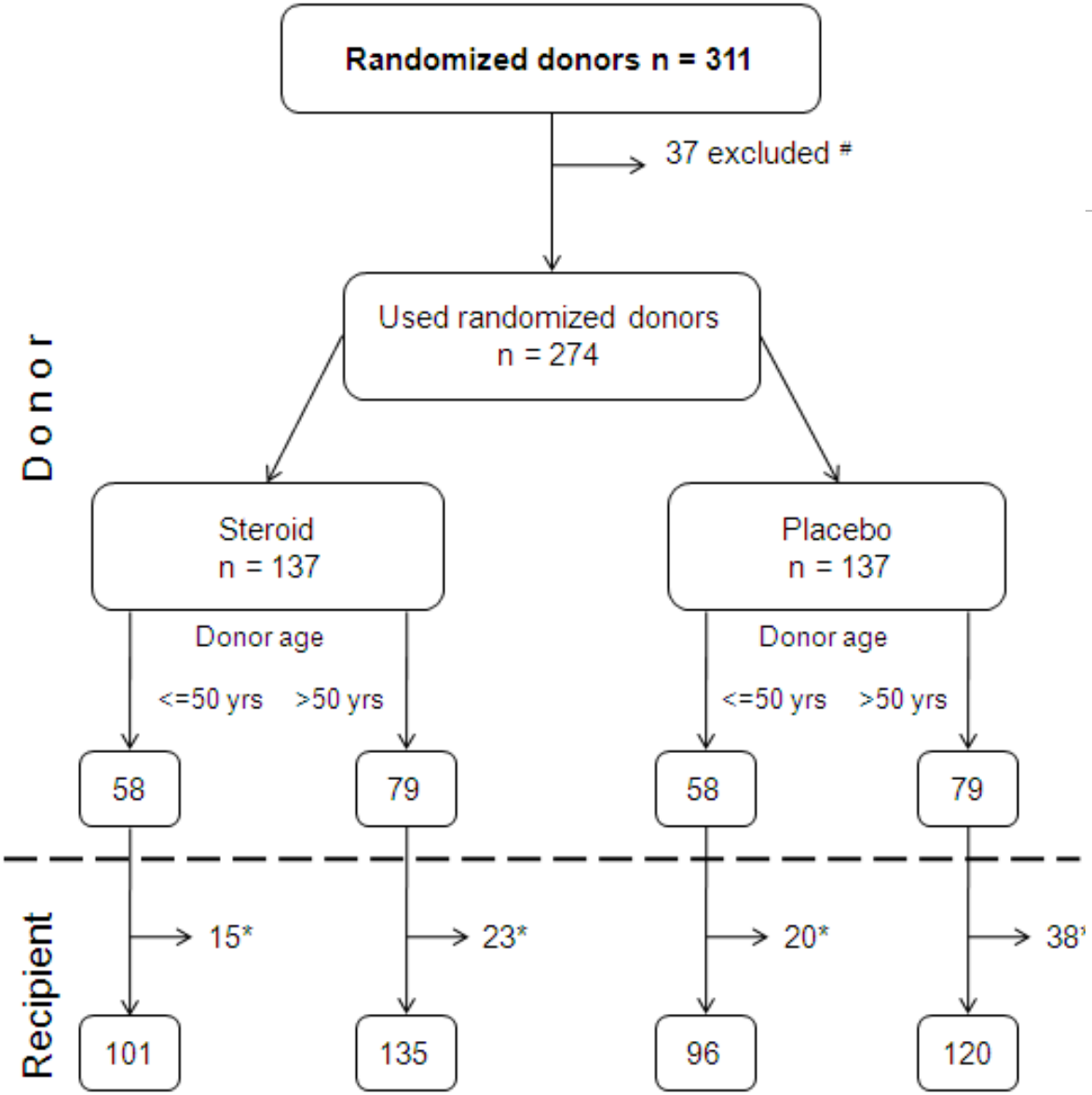
176

Donor sample size

$N^*=N(1/1-LFU/NU)^2=$

$=176(1/.92)^2=207$

Ann Intern Med. 2010;153:222-230



Ann Intern Med. 2010;153:222-230

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Demography of the 274 donors & 458 recipients

Variable	Steroid	Placebo	p-value
Number of donors	137	137	na
Donor age (years)	47.1 (15.1)	48.5 (14.0)	0.452
Donor sex (f/m)	62/74	57/76	0.652
Last creatinine of donor (mg/dl)	0.89 (0.29)	0.90 (0.39)	0.840
Vasopressors used (n/y)	22/114	12/121	0.078
Multiorgan donors (n/y)	106/30	94/39	0.173
Number of recipients	239	219	na
Recipient age (years)	49.6 (14.4)	49.2 (13.9)	0.753
Recipient sex (f/m)	76/162	77/142	0.465
Transplant number (1/2/3/4/5)	204/23/8/2/1	194/21/4/0/0	0.505*
Cold ischemic time (hours)	16.9 (13.4)	16.9 (15.2)	0.995
PRA latest (%)	6 (17)	4 (12)	0.172
Sum of HLA mismatches	3 (1)	3 (1)	0.379
Immunosuppression (CNI/else)	223/15	205/14	0.969
Induction therapy (none/antiCD25/ATG)	143/83/12	126/86/7	0.437

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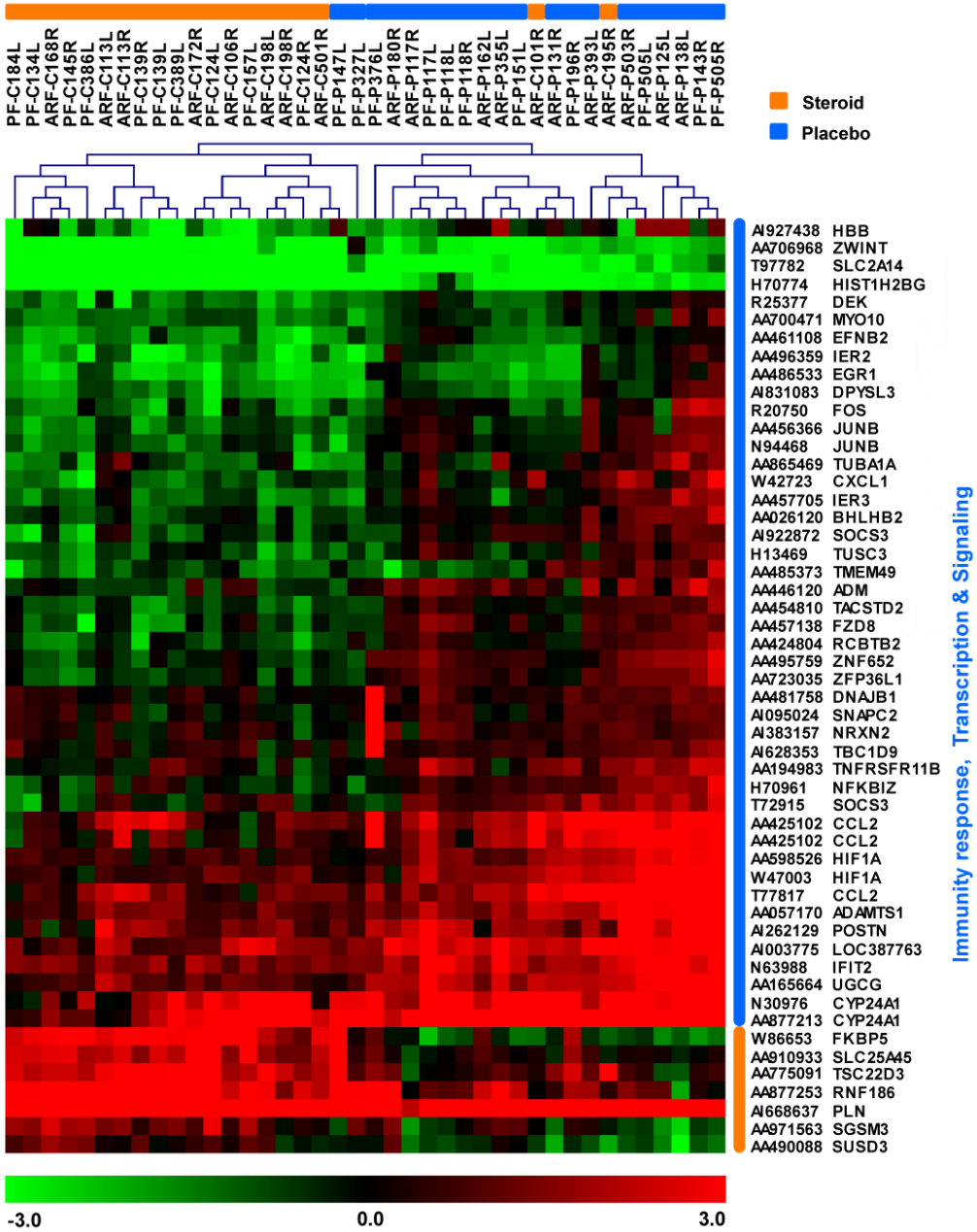
Steroid treatment suppressed inflammation



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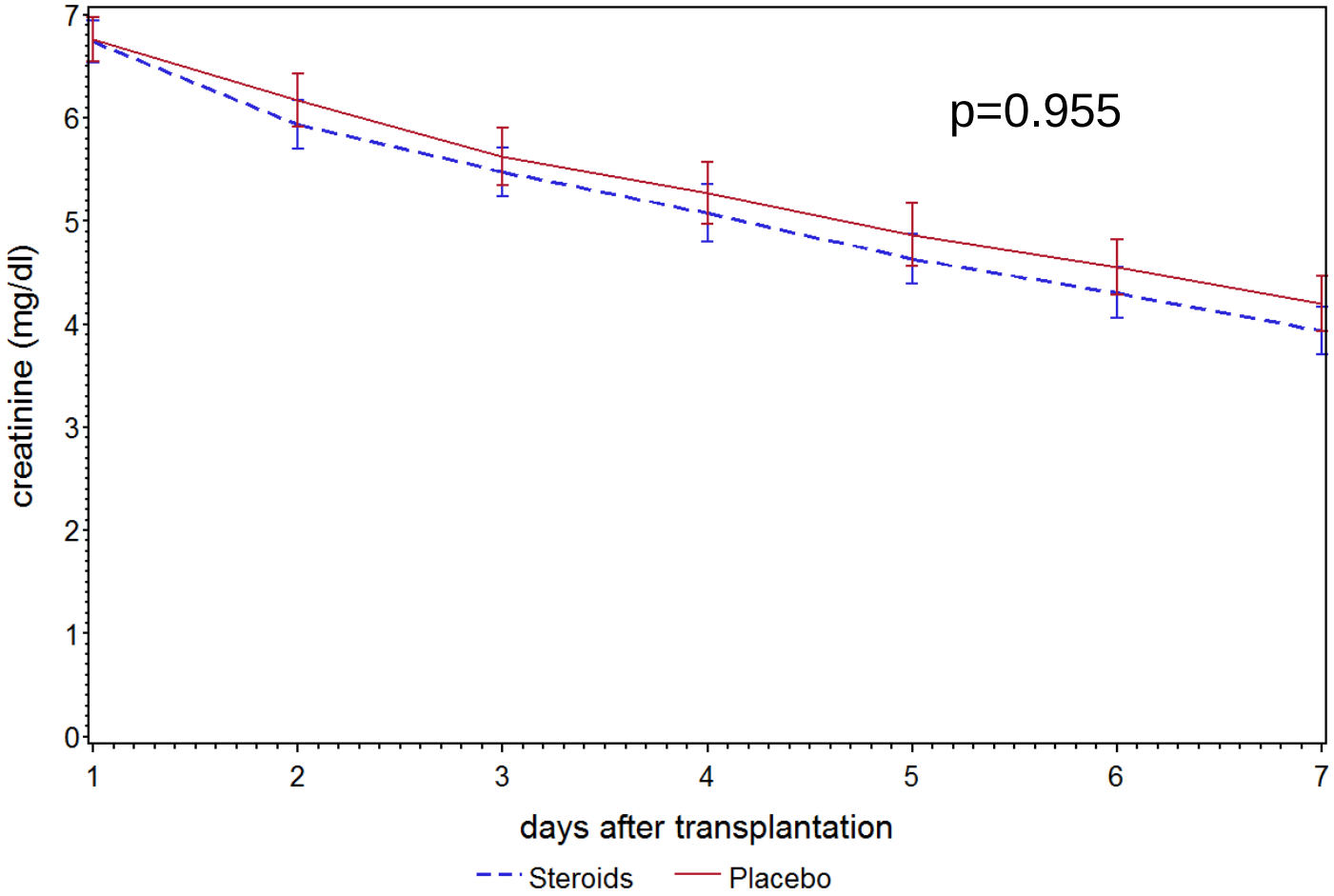
Primary study end point - DGF

	Steroids	Placebo	p-value
% Pts requiring dialysis during the first 7 days (0/1/>1)	65/13/22	63/12/25	0.700
Number of dialysis during the first 7 days (0/1/2/3/4/5)	154/32/18/28/2/4	137/27/27/18/8/2	0.115

Ann Intern Med. 2010;153:222-230

Creatinine Trajectories



Ann Intern Med. 2010;153:222-230

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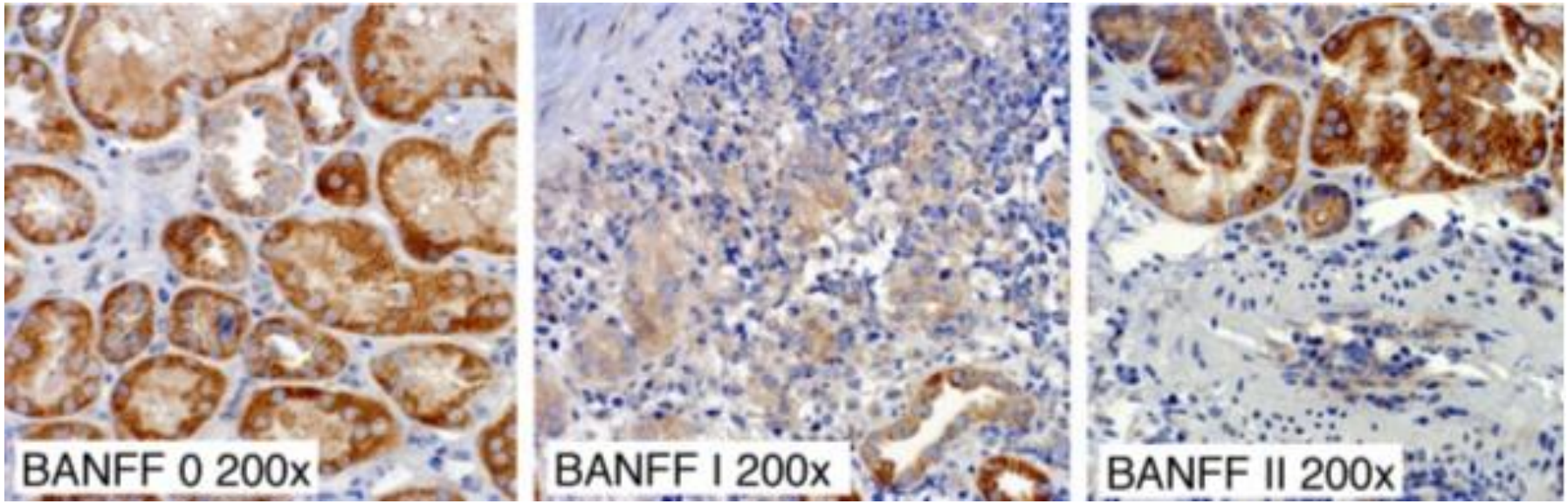
miRNA regulation of kidney injury (FWF P21436 - €250k 2010-2012)

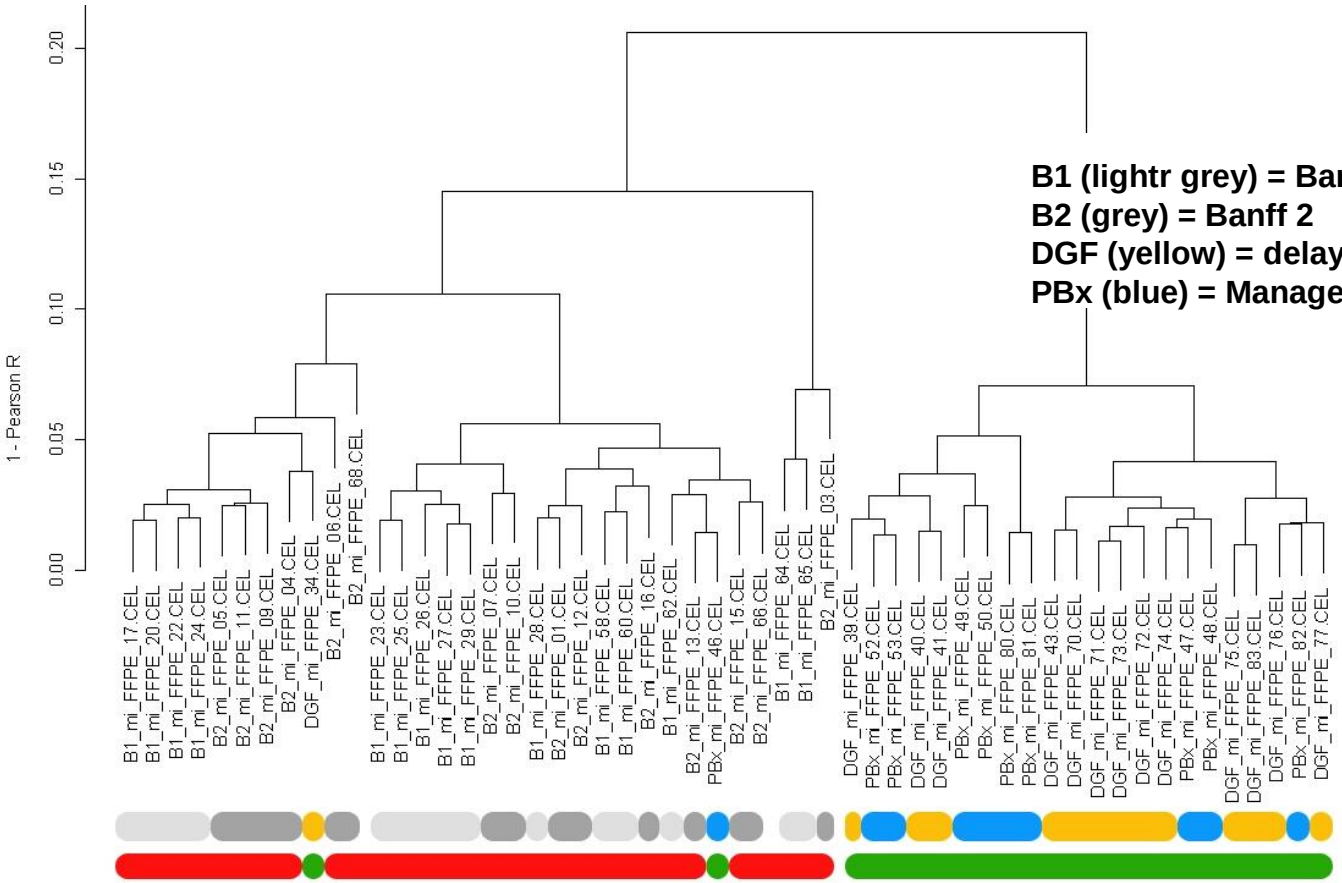


DICER

code for a complex cellular phenotype by silencing of target mRNAs

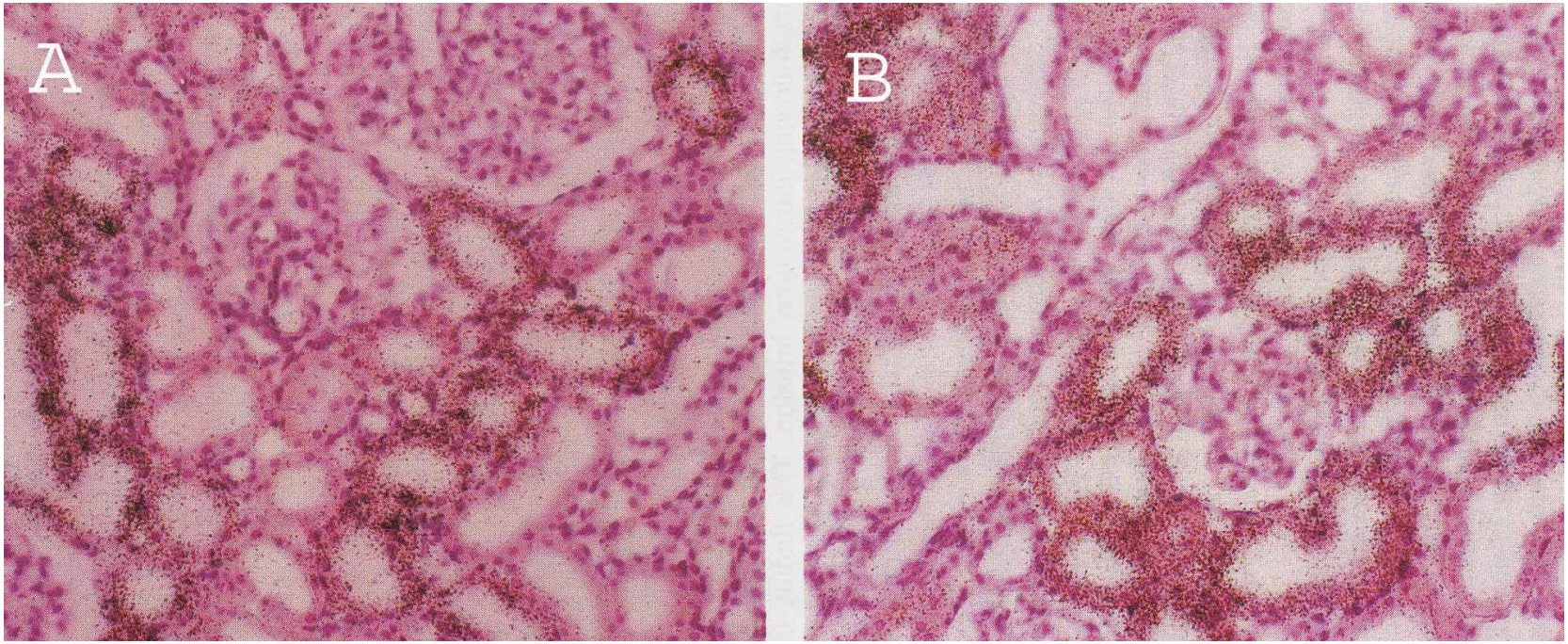
Soleiman A 2009

Differential regulation of miRNAs in delayed graft function – several target genes (miRANDA)



Wilflingseder J et al. 2010

Antisense DNA/siRNA



Oberbauer R et al. Kidney Int 1995, 48:1226-1232

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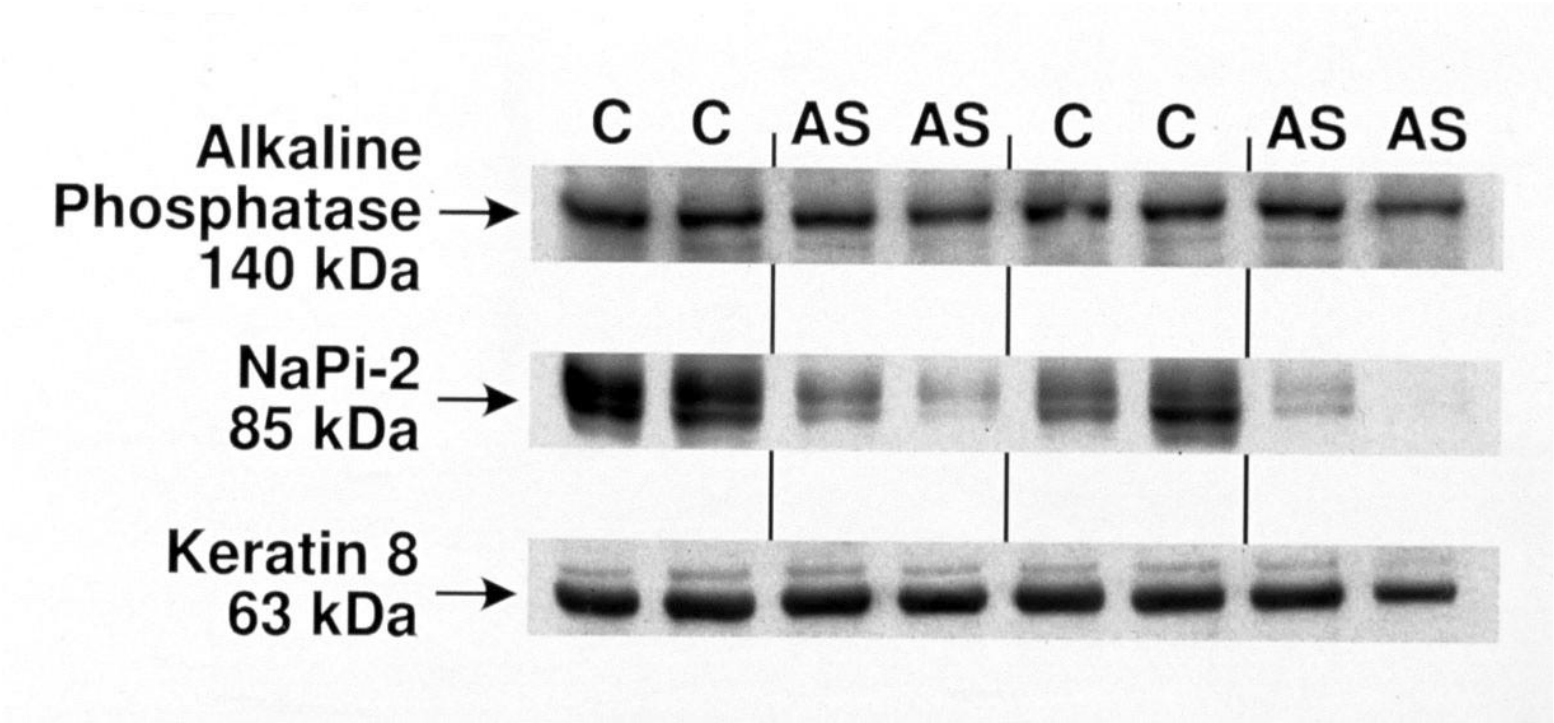
Antisense DNA/siRNA



Oberbauer R et al. PNAS, 1996, 93:4903-4906

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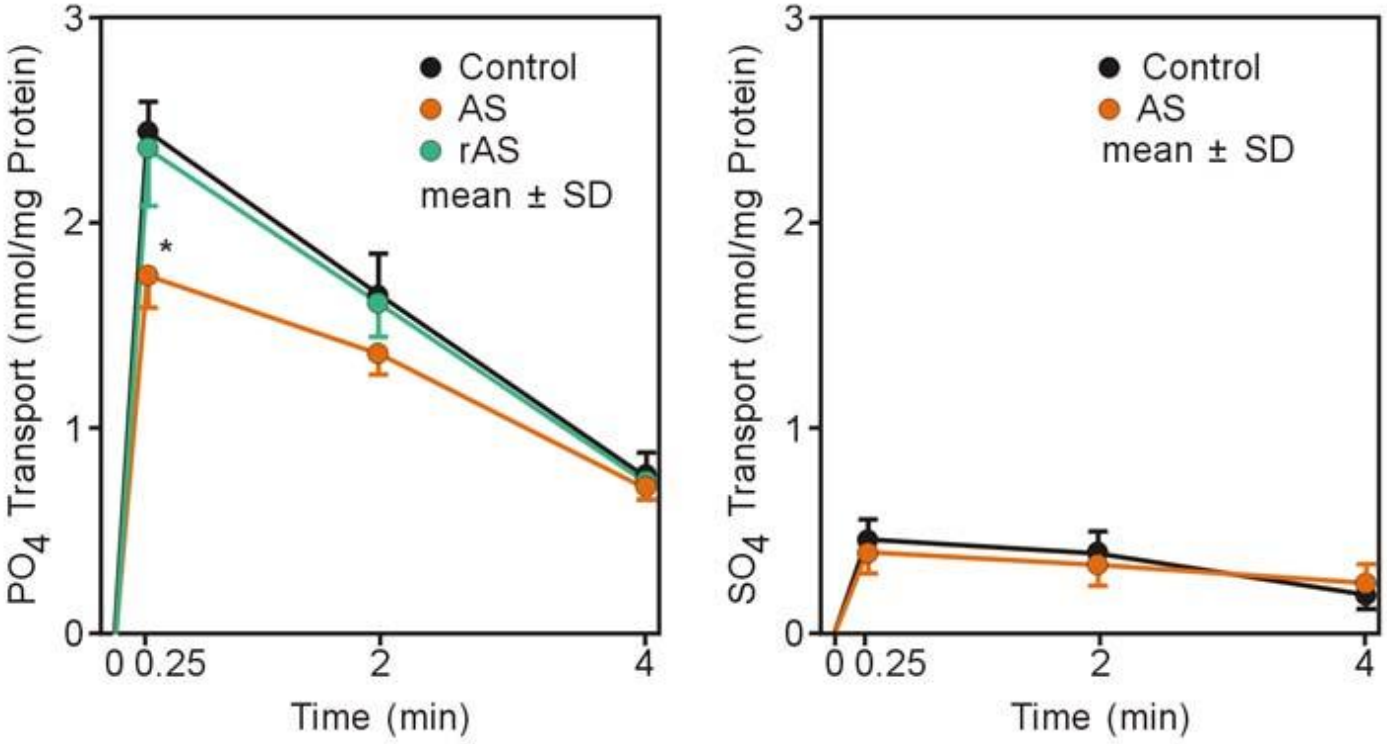
Antisense DNA/siRNA



Oberbauer R et al. PNAS, 1996, 93:4903-4906

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University Zürich — Heini Murer, Jürg Biber

University Vienna — Christoph Schwarz, Christa Mitterbauer, Peter Hauser, Paul Perco, Alexander Kainz, Elisabeth Peherstorfer, Heinz Regele, Dontscho Kerjaschki, Ferdinand Mühlbacher, Walter H. Hörl

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Medical University Vienna

KH Elisabethinen

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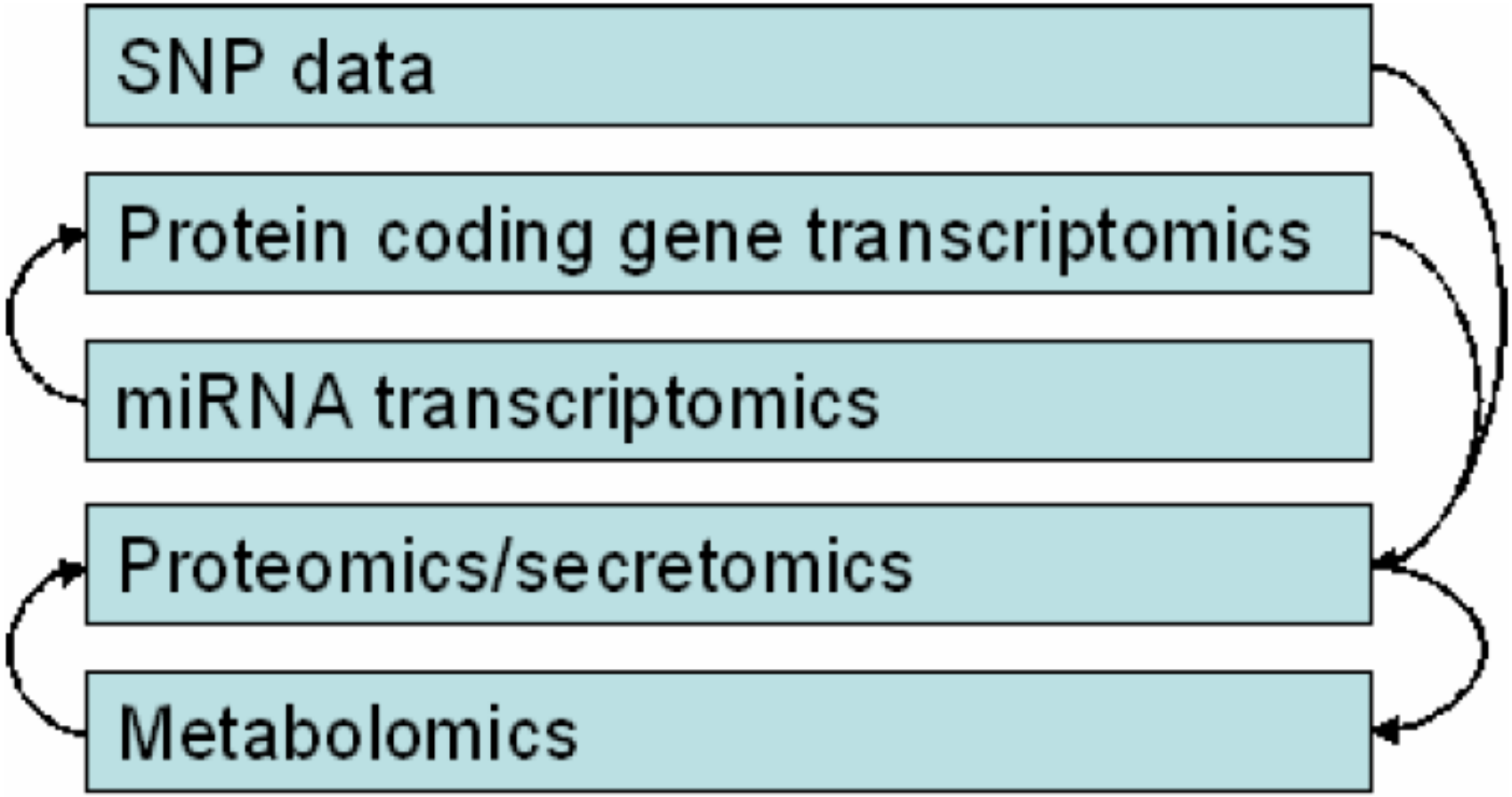
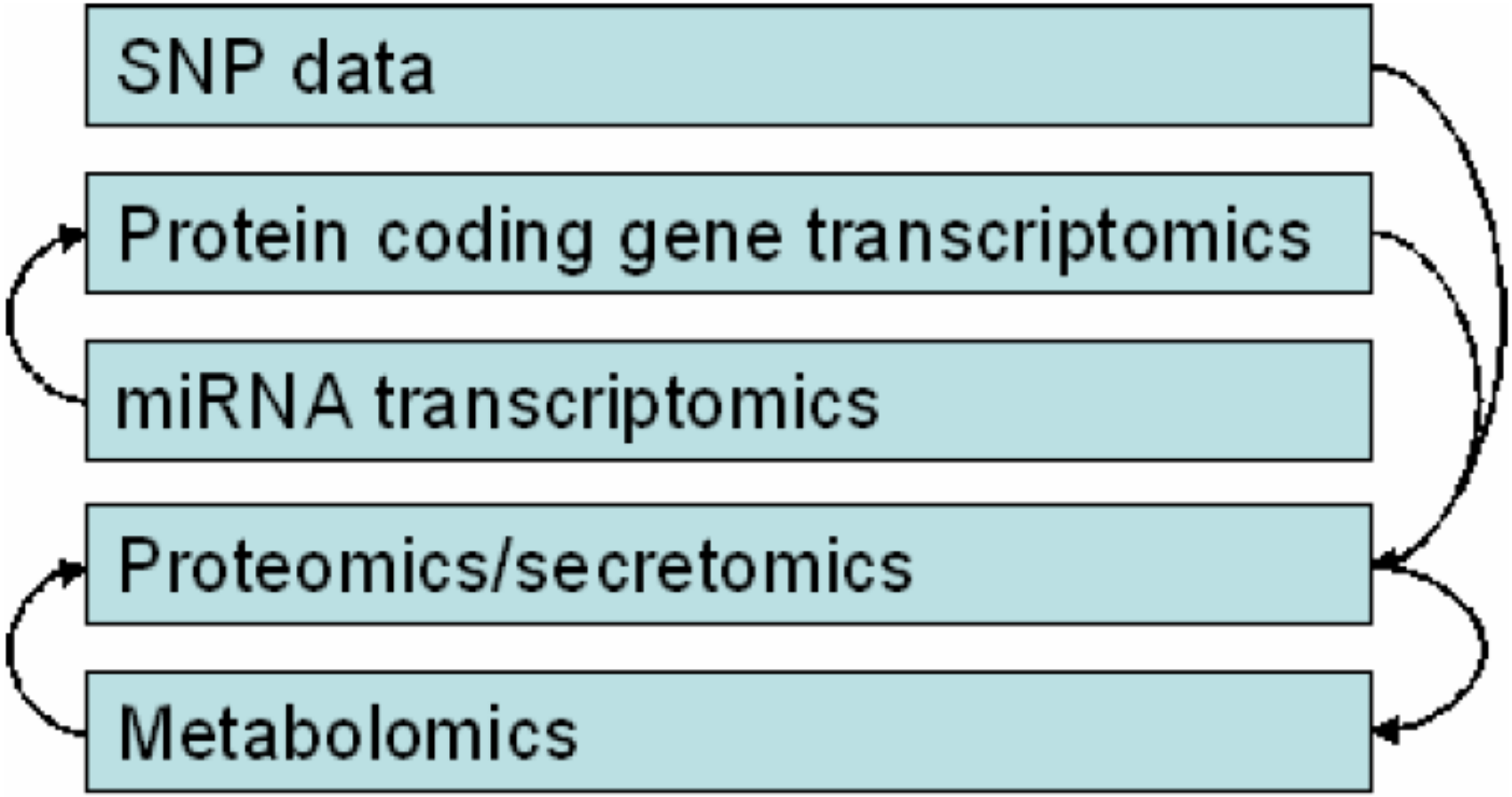
SysKID - Approach



SysKID – Outlook till 2015



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SysKID - Partners

No.	Team Leader	Participant Organization Name	Country	Short Name
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4	Harald Mischak	Mosaiques Diagnostics GmbH	Germany	MOS
5	Barbara Ritzert	Proscience communications GmbH	Germany	PROSCI
6	Peter Rossing	STENO Center Denmark	Denmark	STENO
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19	Doron Lancet	Weizmann Institute of Science	Israel	WIS
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23	Josep Grinyo	Fundacio Privada Institut d'Investigació Biomedica de Bellvitge	Spain	IDIBELL
24	Mourad Farouk	Amgen Europe GmbH	Switzerland	AMGEN
25	Gerhard Hawa	Biomarker design Forschung GmbH	Austria	BMDF

***sysKID* Advisory Board:**

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A2	Steve Ledbetter	Genzyme Corporation	USA
A3	Harry Holthöfer	Dublin City University, Center for Bioanalytical Sciences	Ireland
A4	Wolfgang Winkelmayer	Harvard University Medical School, Department of Nephrology	USA
A5	Timothy Meyer	Stanford University School of Medicine, Department of Nephrology	USA
A6	Matthias Kretzler	University of Michigan, PI of the Nephromine database	USA
A7	Salim Yusuf	Mc Master University, Population Health Research Institute, PI of the ONTARGET study	Canada
A8	Mark Murphy	CEAPIR: European Kidney Patients' Federation	Ireland
A9	Emily Dimmer	EMBL-EBI Cambridge, Gene Ontology Annotation Group	UK

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Conclusions

- GWAS – sample size?
- Genomics – well established
- Proteomics
- Interactome
- In silico mining

Omics in Transplantation – Banff August 2009

2:15 - 2:30	**Liver**: Discussion	Open to all participants
2:30 - 3:00	**Kidney**: Predictors of outcome in ABMR	Denis Glotz
2:30 - 3:00	**Liver**: The spectrum of findings in protocol and indicated biopsies in long-term liver allograft recipients with an emphasis on diagnostic challenges	Stefan Hubscher
3:00 - 3:30	Coffee Break	
3:30 - 4:00	**Kidney**: Does graft accommodation really occur? Mechanisms and long term outcomes	James Gloor
3:30 - 3:45	**Liver**: Discussion	Open to all participants
3:45 - 4:15	**Liver**: Biomarker prediction of successful weaning of liver allograft recipients	Alberto Sanchez Fueyo
4:00 - 4:30	**Kidney**: Analysis of renal transplant protocol biopsies in ABO-incompatible kidney transplantation	Kazunari Tanabe
4:15 - 4:30	**Liver**: Discussion	Open to all participants
4:30 - 5:00	**Kidney**: Diagnosis of AMR - controversies and implications from the clinicians (medical –surgical) point of view	Millie Samaniego
4:30 - 5:00	**Liver**: Complete withdrawal of immunosuppresion in liver transplantation	George Mazariegos
5:00 - 5:15	**Discussion**	
7:00 - 9:00	**Case Presentations from Various Organs with Wine & Cheese**	

WEDNESDAY 12 AUGUST 2009 (Day 3)

Time	Topic	Speaker
	Plenary Session: Surrogate/Non-invasive markers in transplantation	***Kim Solez, Gunilla Einecke***
	Concurrent Morning Session: Heart: Antibody mediated rejection in heart transplantation	***Rene Rodriguez, Adriana Zeevi***
8:00 - 8:05	**Heart**: Introduction and goals for the session	Rene Rodriguez, Adriana Zeevi
8:05 - 8:30	**Heart**: Gene expression in AMR - the Edmonton data from 100 microarrays of heart allograft biopsies	Banu Sis
8:00 - 8:30	**Plenary Session**: Non-invasive prediction of acute rejection in renal allografts	Manikkam Suthanthiran
8:30 - 9:00	**Plenary Session**: Genomics and outcomes after renal transplantation	Rainer Oberbauer
8:30 - 8:50	**Heart**: Markers of antibody mediated rejection and accommodation in heart transplantation	Rene Rodriguez
8:50 - 9:30	**Heart**: Antibodies and the cardiac allograft: types, temporal appearance and minimum follow-up data points to assess a trend. How to interpret in conjunction with the clinical and pathology team	Adriana Zeevi, Nancy Reinsmoen
9:00 - 9:30	**Plenary Session**: Allo-specific cells as non-invasive markers of rejection risk and immunosuppressive effect	Rakesh Sindhi
9:30 - 10:00	**Plenary Session**: Urine proteomics in chronic allograft dysfunction	Josep Campistol
9:30 - 9:50	**Heart**: Diagnosis of AMR - controversies and implications from the clinicians (medical –surgical) point of view	Boudi Kfoury
10:00 - 10:30	**Coffee Break**	
10:30 - 10:45	**Heart**: AMR Current Practice Survey - Europe	Margaret Burke, Annalisa Angelini
10:45 - 11:00	**Heart**: AMR Current Practice Survey - North America	Marc Halushka
10:30 - 11:00	**Plenary Session**: Non-invasive approaches to diagnosis in liver allografts	Hans Pratschke

Omics in Transplantation – Banff August 2009

FRIDAY 14 AUGUST 2009 (Day 5)

Time	Topic	Speaker
	Plenary Session: Summary of organ sessions	***Mark Haas, Bob Colvin***
7:30 - 8:00	Kidney	Lorraine Racusen
8:00 - 8:10	BKN consensus classification summary	Volker Nickeleit
8:10 - 8:40	Pancreas	Cinthia Drachenberg
8:40 - 9:10	Heart	Rene Rodriguez
9:10 - 9:40	Liver	Jake Demetris
9:40 - 10:10	Composite Tissue	Linda Cendales
10:00 - 10:30	**Coffee Break**	
10:30 - 11:00	Omics Technologies	Phil Halloran
11:00 - 11:30	Virtual microscopy as a tool for QA in transplantation pathology: report of a Banff working group	Mark Haas, Banu Sis
11:30 - 12:00	**Key Note Lecture** - "The Banff classification for allograft pathology: where we started, where we are now, where we will go"	Phil Halloran
12:00 - 1:00	**Lunch at Rimrock Resort Hotel**	
1:30	Bus departs for Banff Centre	Location: Meet in Rimrock Lobby
2:15 - 2:30	Tour of the first Banff Conference location	
2:30 - 3:00	**"Nutri-Break" Snack Break**	Location: Max Bell Central Foyer
	Session: Telepathology	***Jake Demetris***
3:00 - 3:30	Digital pathology: problems, promises and application to transplantation	Jake Demetris
3:30 - 4:00	Medical-legal aspects of telepathology	Stanley Leung
4:00 - 4:30	The vision and workflow dynamics of omnyx digital pathology solutions	Tony Melanson
4:30 - 5:00	New developments in digital pathology and Zeiss imaging solutions	Andrew Lesniak
5:00 - 5:30	**Coffee Break**	
5:30 - 7:30	**Farewell Outdoor Barbecue Dinner**	

omics datasets

Transcriptomics

Kainz 2004, Am J Transpl 4:1595-604
Mueller 2009 Am J Transpl 8:78-85
Mas 2008 Transplantation 85(4):626-35

Rudnicki 2007, Kidney Int 71:325-35
Schmid 2006, Diabetes 55:2993-3003
Baelde 2004, Am J Kidney Dis 43:636-50

	AKI	CKD	Total
Transcriptomics	260	699	959
Proteomics	-	34	34
Metabolomics	14	40	54
Total	**274**	**773**	**1047**

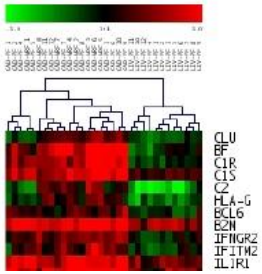
Proteomics
Rossing 2008
JASN 19:1283-90

Metabolomics
Wishart 2009
Nucleic Acids Res
37:D603-10

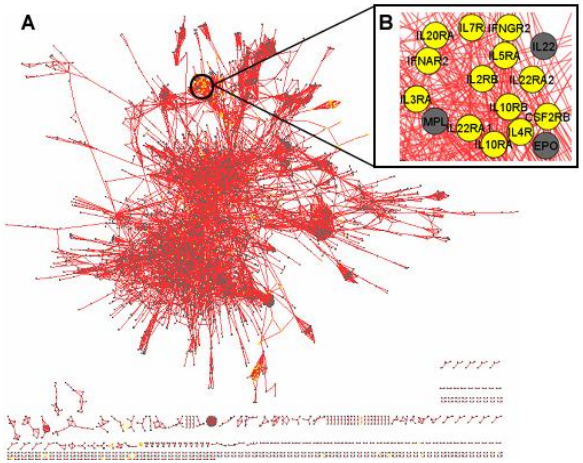
omics features

omicsNET analysis framework

patient disease data



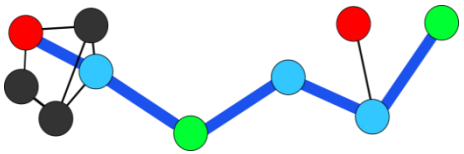
interaction data



gene expression data

functional annotation

subcellular location



molecular subgraphs

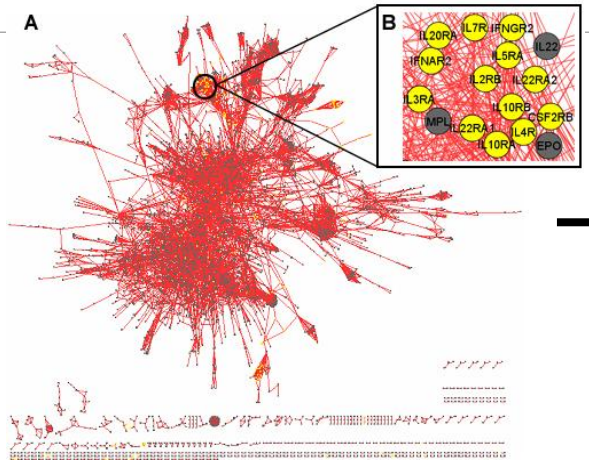
Bernthaler 2009, Mol Biosyst, Jun 3 [ahead of print]

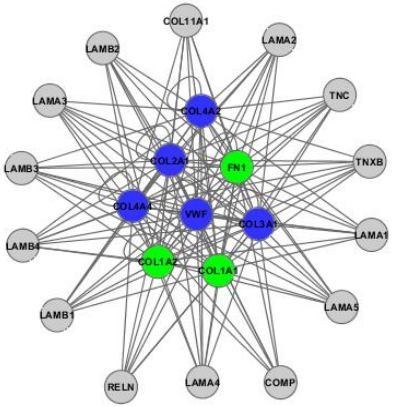
direct overlap

AKI vs CKD: 33 joint features

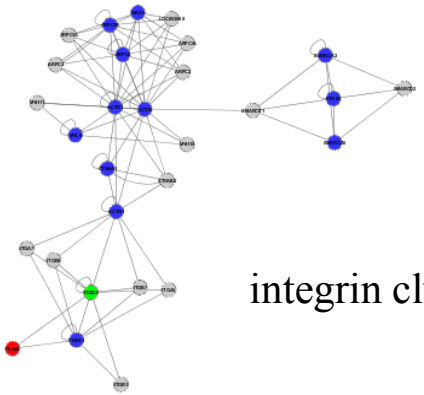
Biological processes	#	P-value	
Cell adhesion	9	< 0.001	e.g. COL1A1, FN1, ITGB3
Cell structure and motility	9	< 0.001	e.g. COL1A1, COL1A2
Protein metabolism and modification	12	< 0.001	e.g. SERPINA5, CASP1
Immunity and defense	7	< 0.001	e.g. TNFSF10, CXCL11

omicsNET networks

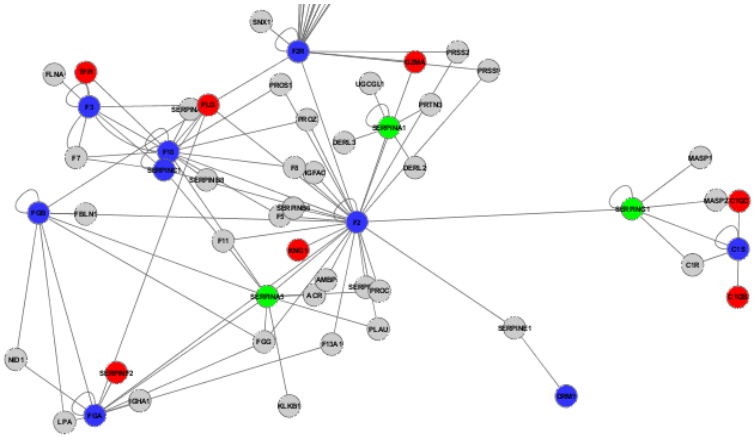




collagen cluster

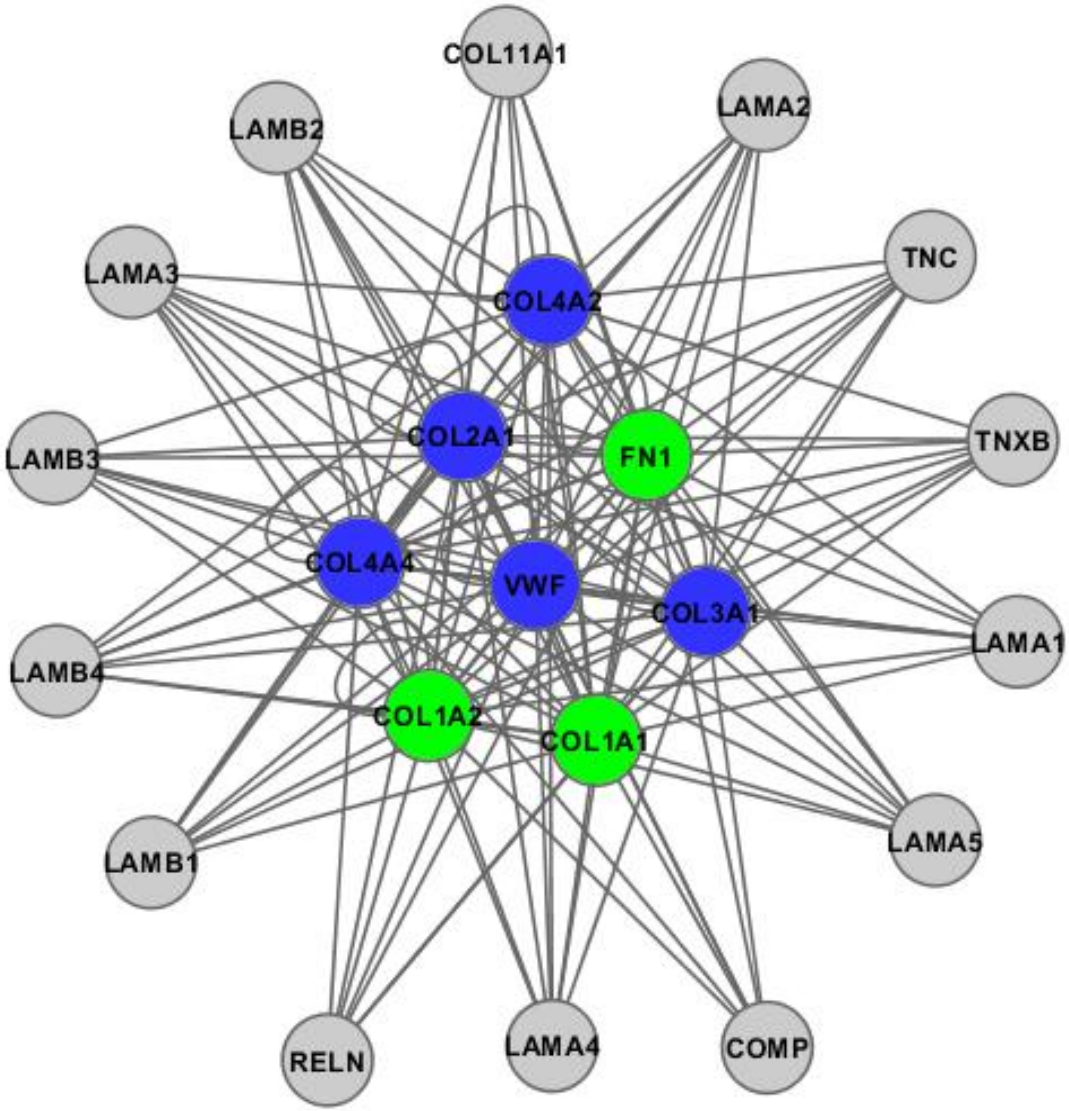


integrin cluster



immune cluster

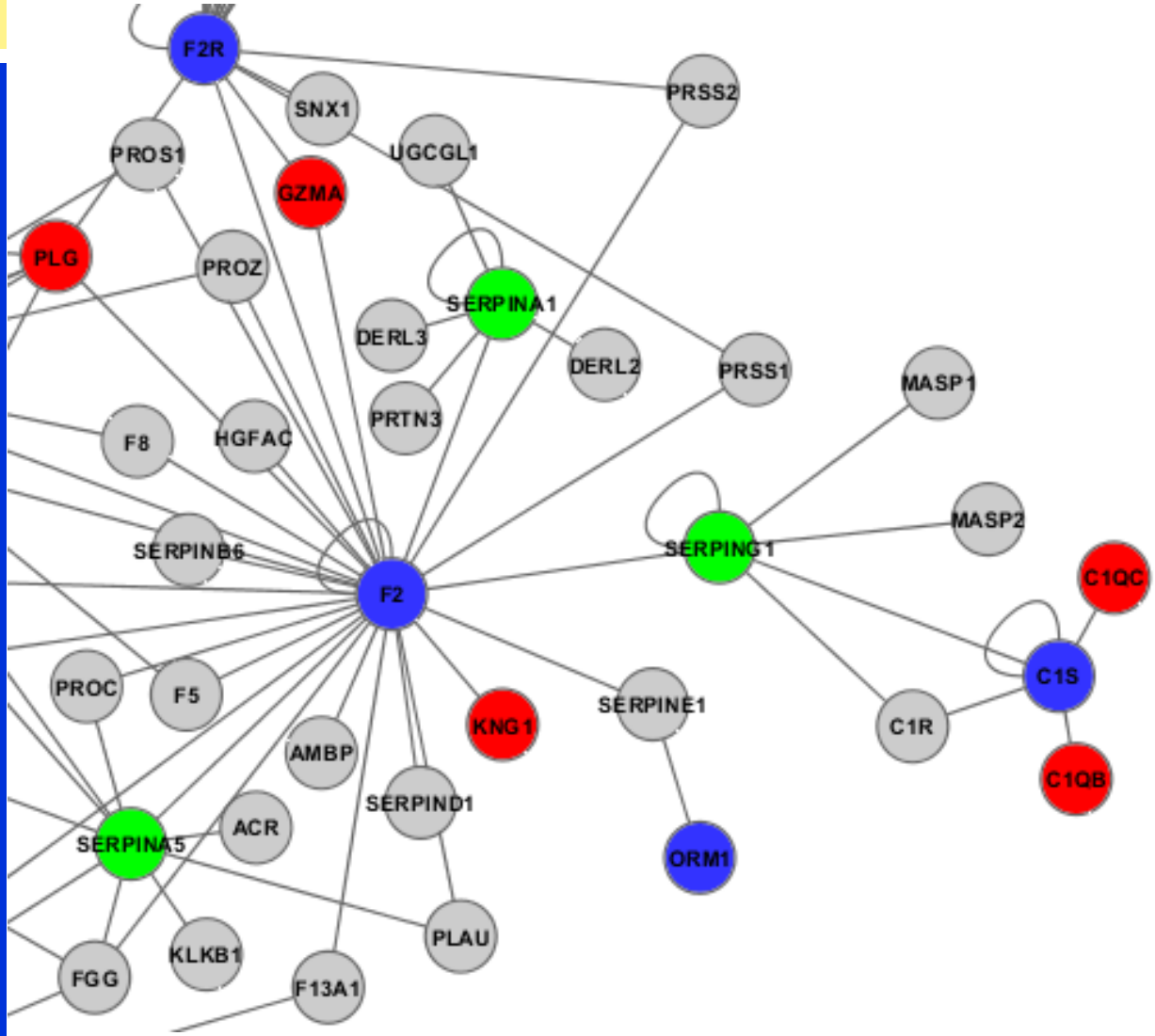
collagen cluster



CKD

AKI + CKD

immune cluster

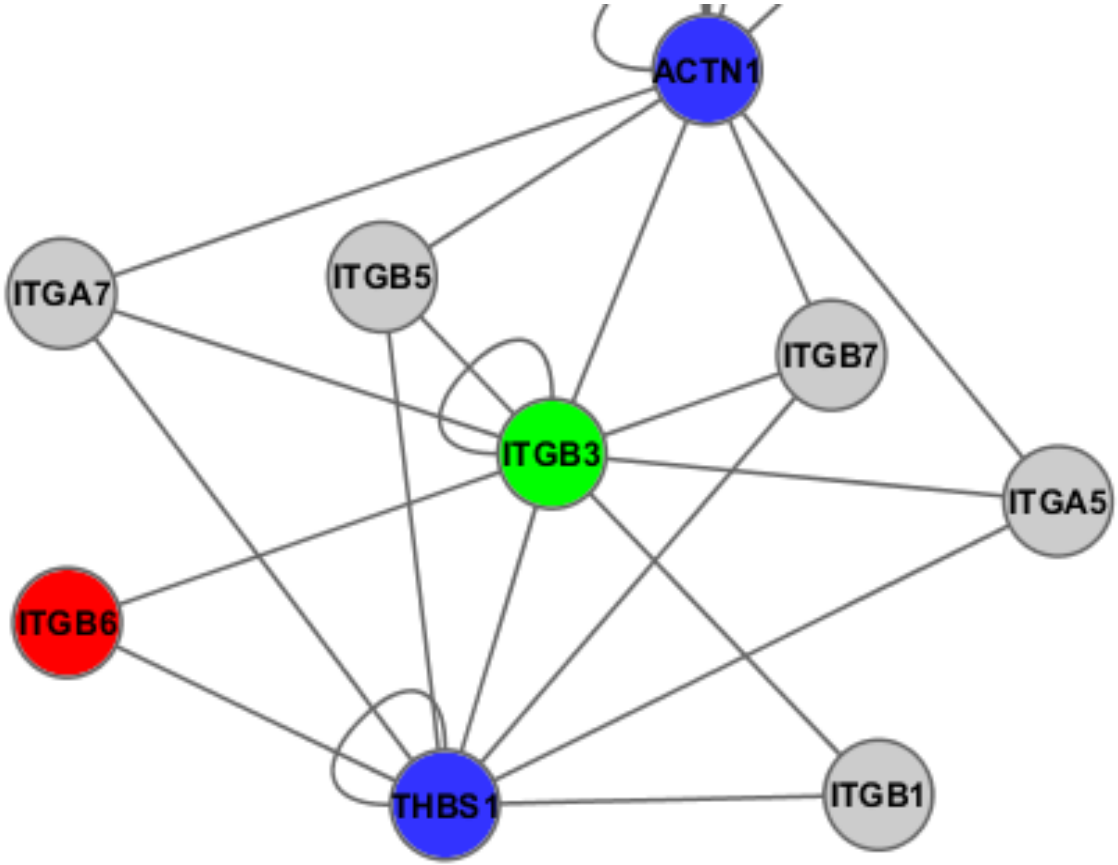


AKI

CKD

AKI + CKD

integrin cluster

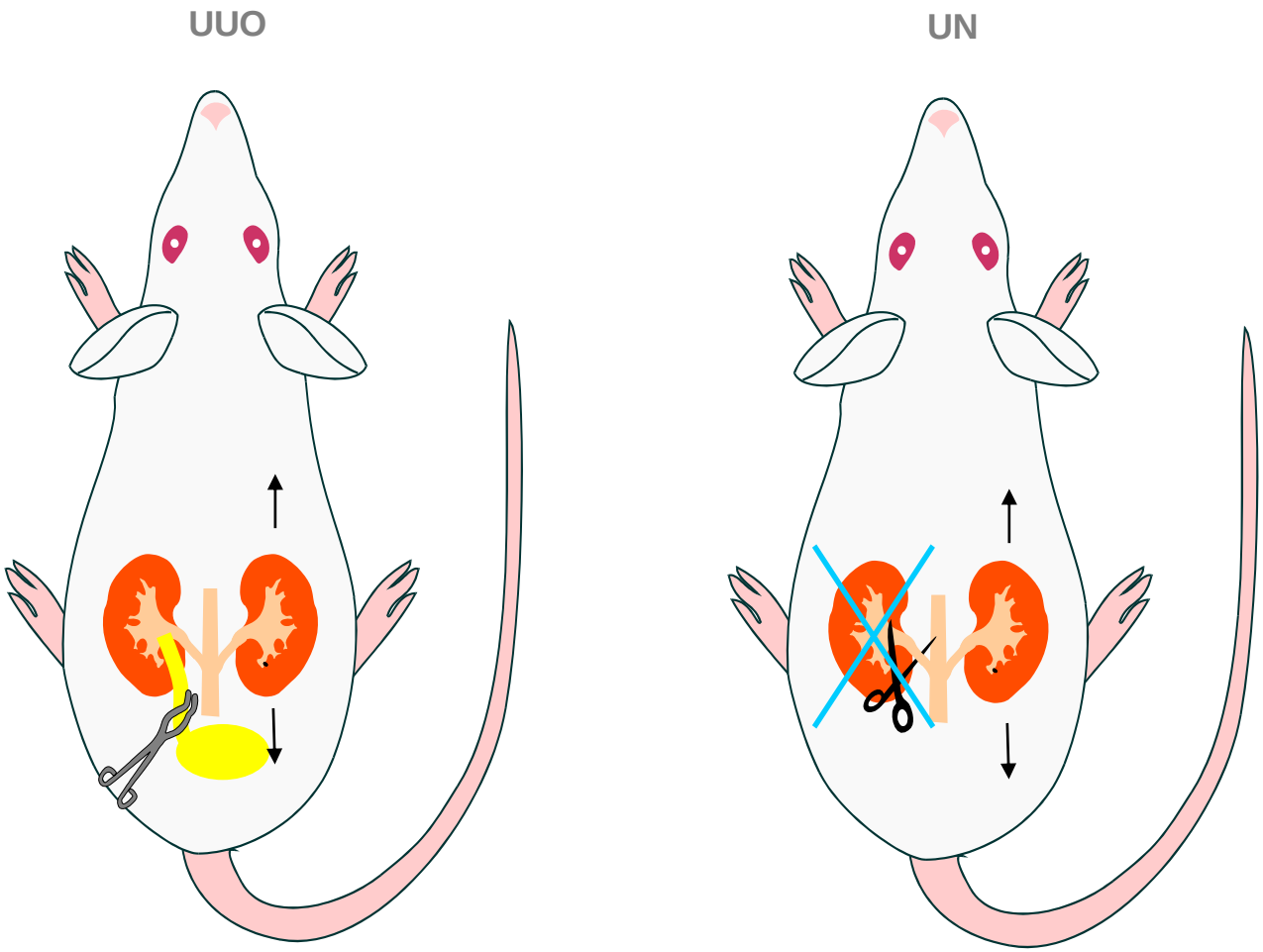


AKI

CKD

AKI + CKD

Response to unilateral ARF



Hauser P et al. *Kidney Int*; Vol. 68 (2005), 2497–2507

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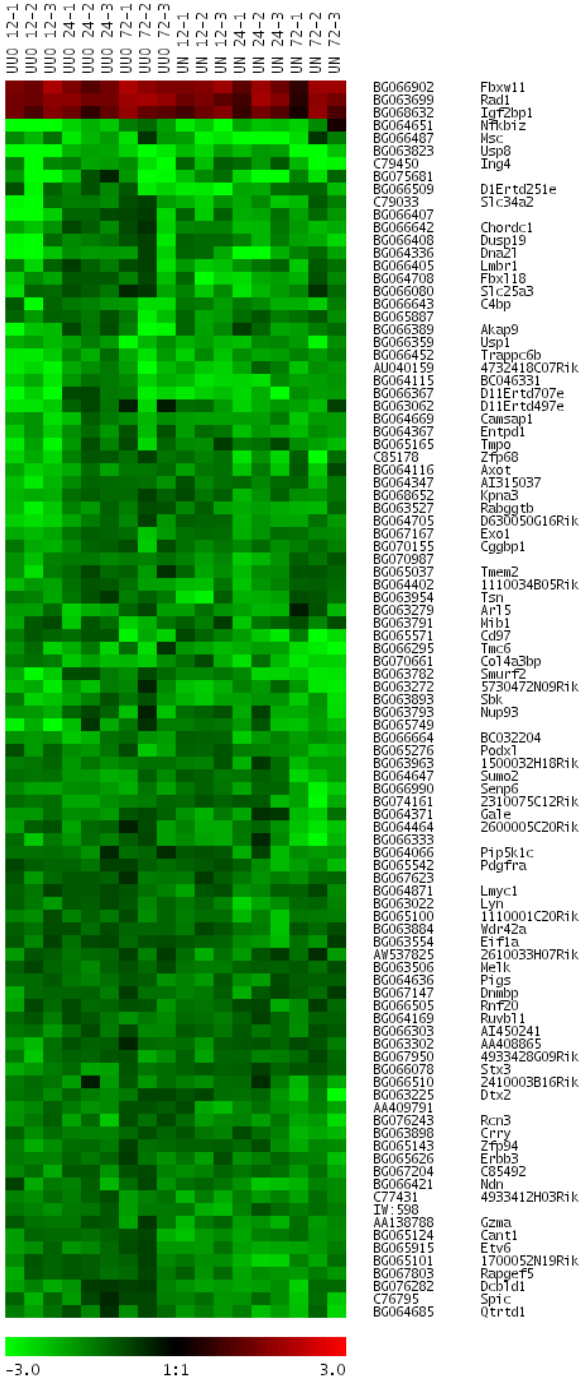

Hauser P et al. *Kidney Int*; Vol. 68 (2005), 2497–2507

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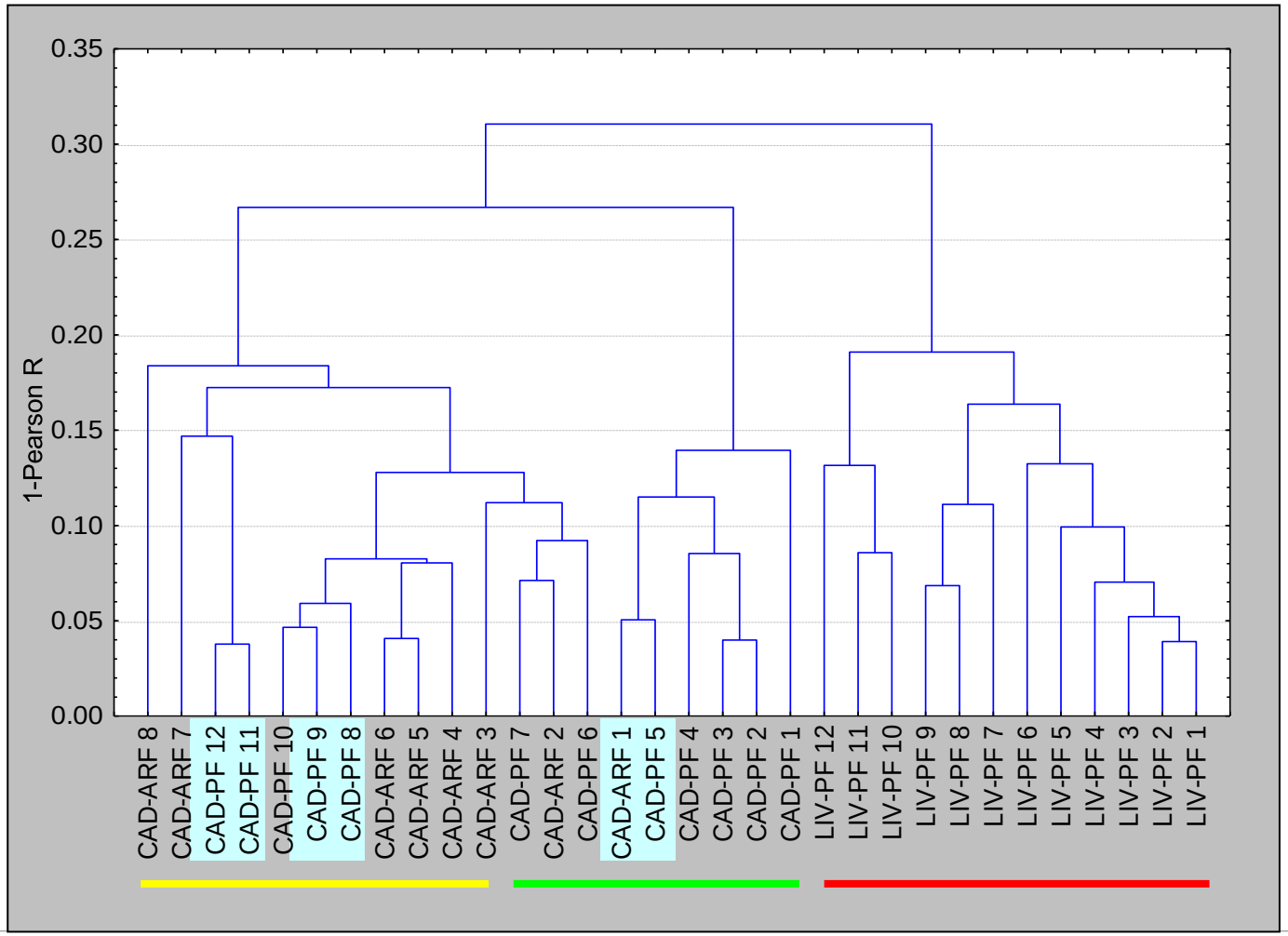
Prediction of DGF/PGF: Unsupervised Clustering of 36 Donor Kidney Biopsies



Hauser P et al, Lab Invest *2004, 84:353-61*

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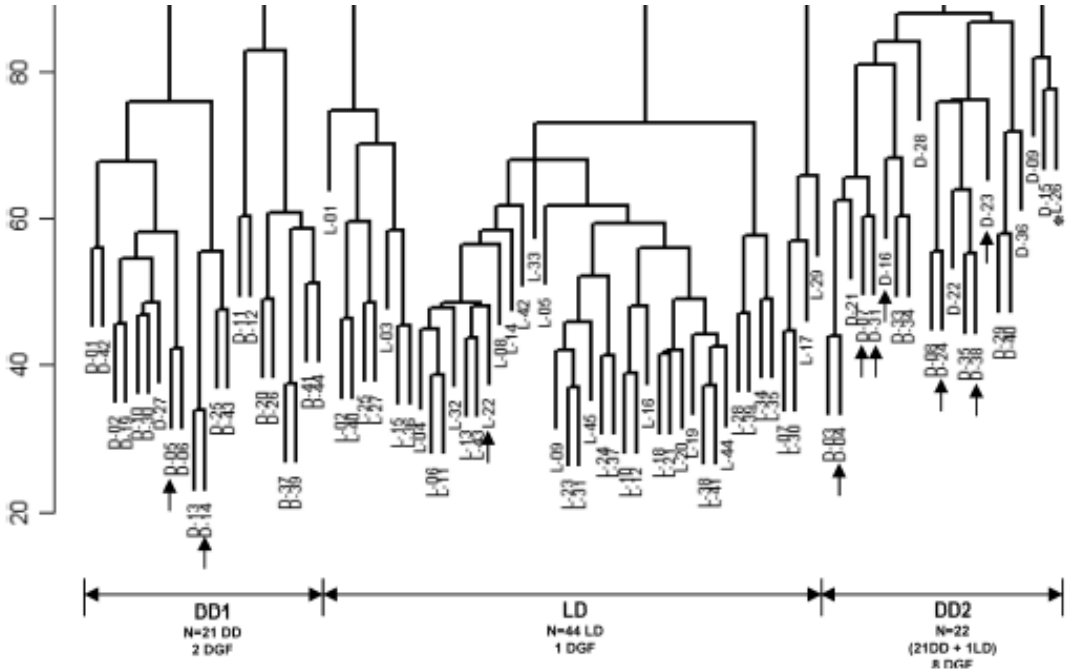
Prediction of DGF/PGF: Unsupervised Clustering of 87 Donor Kidney Biopsies



	Univariate		Multivariate	
Variables	OR[1] (95% CI)[2]	p	OR[1] (95% CI)[2]	p
Recipient age >55 yrs	6.67 (1.21–36.74)	0.029	9.14 (1.33–62.63)	0.024
Principal component score PC1	1.05 (1.01–1.10)	0.025	1.06 (1.01–1.12)	0.022
'Irish' score[3]	1.02 (0.96–1.07)	0.576		
'Schold' score[4]	2.21 (0.19–25.83)	0.527		
'Nyberg' score[5]	1.04 (0.91–1.19)	0.605		
Global kidney score[6]	1.18 (0.82–1.70)	0.371		
Banff score total	1.23 (0.84–1.78)	0.284		

Mueller T et al. Am J Transplant. 2008 Jan;8(1):78-85.

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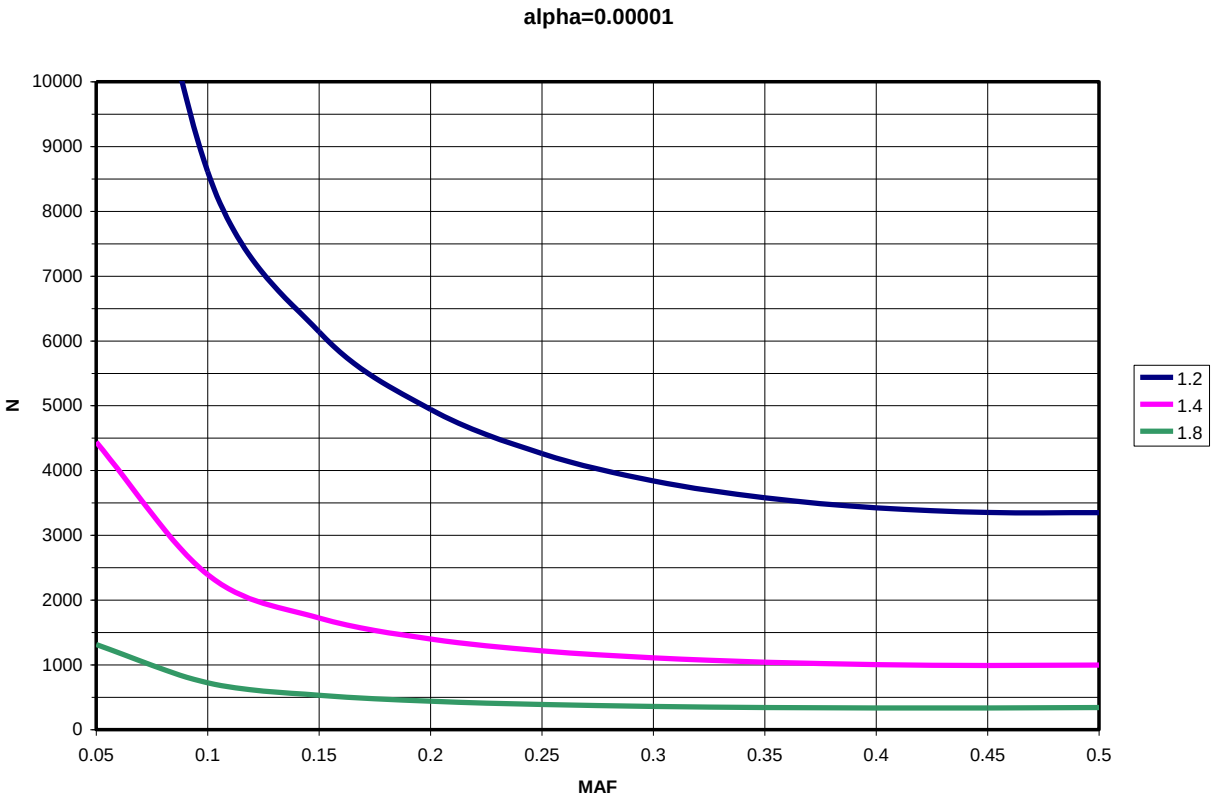
Sample sizes required for genetic association studies



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OMES TABLE

What is Bioinformatics? pdf | 'oming in on function pdf |Bioinformatics class |The OED defines 'ome' |Other 'ome pages |Gerstein lab

Terms	Description	Google Search *	Pubmed Search *	First Year in Pubmed
Genome	The full complement of genetic information both coding and non coding in the organism	1,510,000	70,970	1932
Proteome	The protein-coding regions of the genome	65,600	1096	1995
Transcriptome	The population of mRNA transcripts in the cell, weighted by their expression levels	5750	126	1997
Physiome	Quantitative description of the physiological dynamics or functions of the whole organism	3650	16	1997
Metabolome	The quantitative complement of all the small molecules present in a cell in a specific physiological state	753	13	1998
Phenome	Qualitative identification of the form and function derived from genes, but lacking a quantitative, integrative definition	23,500	8	1995
Morphome	The quantitative description of anatomical structure, biochemical and chemical composition of an intact organism, including its genome, proteome, cell, tissue and organ structures	205	2	1996
Interactome	List of interactions between all macromolecules in a cell	168	4	1999
Glycome	The population of carbohydrate molecules in the cell	77	3	1999
Secretome	The population of gene products that are secreted from the cell	100	4	2000
Translatome	The population of mRNA transcripts in the cell, weighted by their expression levels	41	1	2001
Fluxome	The population of proteins weighted by their fluxes	10	1	1999
Localizome	The localization of various proteins, both in terms of cell type and subcellular compartments	10	-	2001
Pseudome	The population of pseudgenes in the cell	4	-	-
Ribonome	The population of RNA-coding regions of the genome	11	-	-
Orfeome	The sum total of open reading frames in the genome, without regard to whether or not they code; a subset of this is the proteome	418	-	-
Regulome	Genome-wide regulatory network of the cell	36	-	-
Cellome	The entire complement of molecules and their interactions within a cell	27	-	-
Operome	The characterization of proteins with unkown biological function	17	-	-
Transportome	The population of the gene products that are transported; this includes the secretome	9	-	-
Functome	The population of gene products classified by their functions	18	-	-
Foldome	The population of gene products classified by their tertiary structure	11	-	-
unknome	Genes of unkown function	4	-	-

To add new and innovative omes to the list email: dov.greenbaum@yale.edu

*Values as of 02/06/02

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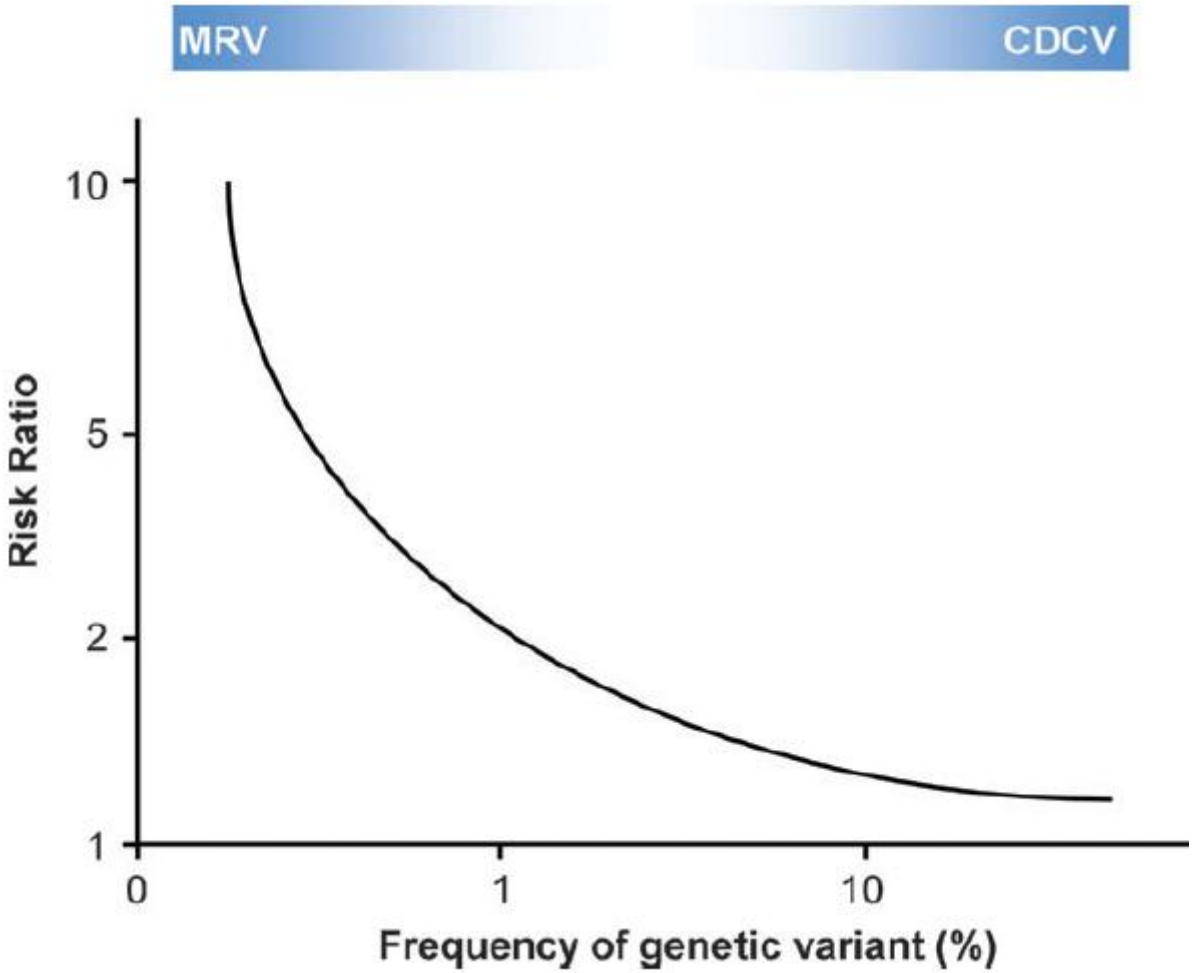
GWAS and outcomes



Pesce F and Schena FP et al. NDT Sept 2009 (epub ahead of print)

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Omics in Transplantation

1: Am J Transplant. 2008 Apr;8(4):753-60. Epub 2008 Feb 19.

Banff 07 classification of renal allograft pathology: updates and future directions.

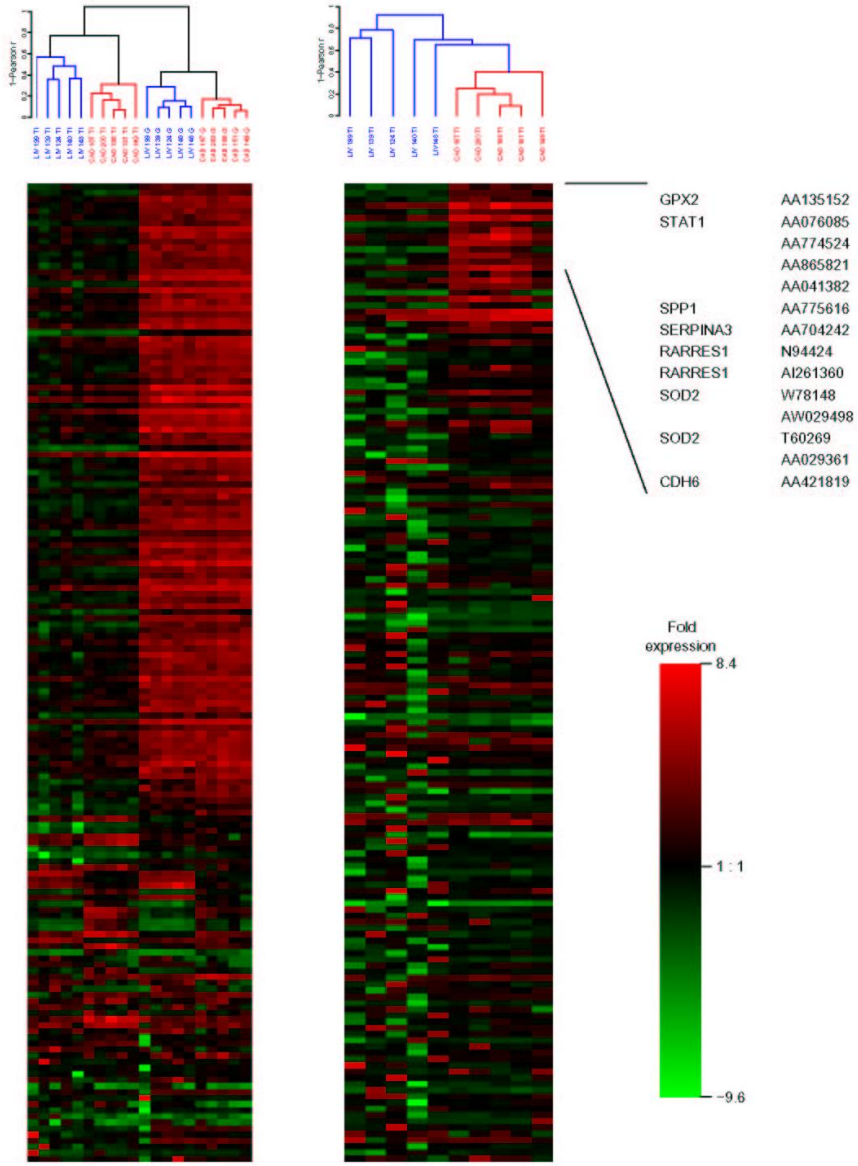
Solez K, Colvin RB, Racusen LC, Haas M, Sis B, Mengel M, Halloran PF, Baldwin W, Banfi G, Collins AB, Cosio F, David DS, Drachenberg C, Einecke G, Fogo AB, Gibson IW, Glotz D, Iskandar SS, Kraus E, Lerut E, Mannon RB, Mihatsch M, Nankivell BJ, Nickeleit V, Papadimitriou JC, Randhawa P, Regele H, Renaudin K, Roberts I, Seron D, Smith RN, Valente M.

Department of Laboratory Medicine and Pathology, University of Alberta, Edmonton, Canada. Kim.Solez@ualberta.ca

The 9th Banff Conference on Allograft Pathology was held in La Coruna, Spain on June 23-29, 2007. A total of 235 pathologists, clinicians and scientists met to address unsolved issues in transplantation and adapt the Banff schema for renal allograft rejection in response to emerging data and technologies. The outcome of the consensus discussions on renal pathology is provided in this article. Major updates from the 2007 Banff Conference were: inclusion of peritubular capillaritis grading, C4d scoring, interpretation of C4d deposition without morphological evidence of active rejection, application of the Banff criteria to zero-time and protocol biopsies and introduction of a new scoring for total interstitial inflammation (ti-score). In addition, emerging research data led to the establishment of collaborative working groups addressing issues like isolated 'v' lesion and incorporation of omics-technologies, paving the way for future combination of graft biopsy and molecular parameters within the Banff process.

PMID: 18294345 [PubMed - indexed for MEDLINE]

Microdissected biopsies of live (blue) and deceased (red) kidney donors



The 113 significant features differentiating TI vs. G are displayed in Webtable 1 (SD ≥ 1.6)

Kainz A et al.

Am J Transplant 2004; 4:1595-1604

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CAD up	NOTES (Pathway)	NOTES(Summary)	GeneSymbol	GeneName	maxT
-	blood coagulation	blood coagulation, synthetized in kidney	PLG	plasminogen	5,00E-04
-	blood coagulation, blood clotting	in plasma, assists hemostasis, 2EGF domains	PROZ	protein Z, vitamin K-dependent plasma glyco	0,0013
+	blood coagulation, blood clotting	blood clotting, cell adhesion, inflammation	VCAM1	vascular cell adhesion molecule 1	0,0041
+	blood coagulation, response to injury	blood coagulation, cell adhesion molecule	FGG	fibrinogen, gamma polypeptide	0,0055
+	cell adhesion	cell adhesion, calcium dependent	CDH6	cadherin 6, type 2, K-cadherin (fetal kidney)	6,00E-04
+	cell adhesion	cell adhesion/recognition,	CSPG2	chondroitin sulfate proteoglycan 2 (versican)	3,00E-04
+	complement	complement lysis inhibitor, associated with APOP	CLU	**clusterin (complement lysis inhibitor, SP-4	0,0072
+	complement, alternat. Way	complement	BF	B-factor, properdin	1,00E-04
+	complement, class. Way	complement	C1R	complement component 1, r subcomponent	1,00E-04
+	complement, class. Way	complement	C1S	complement component 1, s subcomponent	0,0058
+	complement, class. Way	complement	C2	complement component 2	9,00E-04
-	immune response	defense/immunity protein, blood coagulation	APOH	apolipoprotein H (beta-2-glycoprotein I)	0,0257
+	immune response	defense response, MHC	HLA-G	HLA-G histocompatibility antigen, class I, G	0,003
+	immune response	inflammatory response	BCL6	B-cell CLL/lymphoma 6 (zinc finger protein 5	0,0141
+	immune response	MHC I molecule	B2M	beta-2-microglobulin	0,0087
+	immune response	response to viruses, immune response	IFNGR2	interferon gamma receptor 2 (interferon gam	8,00E-04
+	immune response	immune response	IFITM2	interferon induced transmembrane protein 2	0,0137
+	immune response	immune response, inflammatory response	IL1R1	interleukin 1 receptor, type I	0,0076
+	immune response, ion transporter	humoral immune response, iron transport	LTF	lactotransferrin	0,0064
+	immune response	MHC	HLA-DQB1	major histocompatibility complex, class II, D	0,0398
+	immune response	cell adhesion, immune response	NK4	natural killer cell transcript 4	7,00E-04
-	ion transporter	ion transporter, transmembraneous	CLCN4	chloride channel 4	0,002
+	ion transporter	cation transporter, transmembraneous	SLC39A1	solute carrier family 39 (zinc transporter), m	5,00E-04
-	metabolism (AA)	AA and derivative metabolism	BPHL	**biphenyl hydrolase-like (serine hydrolase; I	0,0085
-	metabolism (AA)	AA metabolism	HPD	4-hydroxyphenylpyruvate dioxygenase	0,0062
-	metabolism (AA)	AA metabolism, Urea cycle	ASS	argininosuccinate synthetase	0,0019
-	metabolism (AA)	AA metabolism	PAH	phenylalanine hydroxylase	0,002
-	metabolism (AA), degradation	mitochondrial, AA degradation	HMGCS2	3-hydroxy-3-methylglutaryl-Coenzyme A syn	0,0059
-	metabolism (general)	aldo-keto-reductase	ALDRL6	aldehyde reductase (aldose reductase) like 6	0,0141
-	metabolism (general)	energy pathway	APOM	apolipoprotein M	0,0352
+	metabolism (general)	electron transporter, glutathione metabolism	GPX2	glutathione peroxidase 2 (gastrointestinal)	1,00E-04
+	metabolism (general)	N-Glycans biosynthesis	MAN1C1	mannosidase, alpha, class 1C, member 1	0,0354
-	metabolism (general)	dehydrogenase, oxidoreductase	DHDH	dihydrodiol dehydrogenase (dimeric)	0,0015
-	metabolism (general)	role in the biosynthesis of CoA	PANK1	pantothenate kinase 1	0,0012
-	metabolism (general)	delivers retinol	RBP4	retinol binding protein 4, plasma	0,0211
-	metabolism (lipid)	lipid metabolism, oncogenesis	CYP3A4	cytochrome P450, subfamily IIIA (niphedipine	3,00E-04
-	metabolism (lipid)	lipid metabolism	CYP3A7	cytochrome P450, subfamily IIIA, polypeptide	1,00E-04
+	metabolism (lipid)	lipid metabolism	APOA4	apolipoprotein A-IV	0,0433
-	metabolism (lipid)	fatty acid metabolism	FABP1	fatty acid binding protein 1, liver	0,0118
-	metabolism (lipid, AA)	lipid, AA metabolism, central nervous system deve	ALDH3A2	aldehyde dehydrogenase 3 family, member A	1,00E-04
-	metabolism (sugar)	fructose metabolism, glycolysis	FBP1	fructose-1,6-bisphosphatase 1	0,0098
-	metabolism (sugar)	mitochondrial, glucose metabolism	PCK2	phosphoenolpyruvate carboxykinase 2 (mito	0,0202
-	metabolism (sugar)	fructose/mannose metabolism	SORD	sorbitol dehydrogenase	0,0385
+	metabolism (sugar)	carbohydrate metabolism	GCNT3	glucosaminyl (N-acetyl) transferase 3, mucin	0,0083
+	peptidase inhibitor	peptidase inhibitor	SLPI	secretory leukocyte protease inhibitor (antile	0,022
+	peptidolysis, proteasome	proteasome, proteolysis, peptidolysis, antigen proc	PSMB8	proteasome (prosome, macropain) subunit,	8,00E-04
+	proteinase inhibitor	protease, peptidase inhibitor	SERPINA3	serine (or cysteine) proteinase inhibitor, clad	1,00E-04
+	proteinase inhibitor	protease, peptidase inhibitor	SERPINE2	serine (or cysteine) proteinase inhibitor, clad	0,0196
+	proteinase inhibitor	protease, peptidase inhibitor	SERPING1	serine (or cysteine) proteinase inhibitor, clad	0,0281
-	proteinase inhibitor	peroxisomal, lysine degradation	PIPOX	pipecolic acid oxidase	1,00E-04
-	proteinase inhibitor	membrane, aminopeptidase	XPNPEP2	X-prolyl aminopeptidase (aminopeptidase P)	0,0435
+	proteinase inhibitor	protein modification	QPCT	glutaminyl-peptide cyclotransferase (glutami	6,00E-04
+	proteinase inhibitor	serine/threonine kinase	STK19	serine/threonine kinase 19	1,00E-04
+	proteinase inhibitor	peroxisomal, mitochondrial	AMACR	alpha-methylacyl-CoA racemase	0,0127
+	proteinase inhibitor	lysososme, intracellular protein transport	NPC1	Niemann-Pick disease, type C1	0,0025
+	Reg. of cell prolif (-) (APOPTOSIS ?)	neg. regulation of cell proliferation	RARRES1	**retinoic acid receptor responder (tazaroter	0,039
+	Reg. of cell prolif (-)	neg. regulation of cell proliferation	ADAMTS1	a disintegrin-like and metalloprotease (reprol	0,0195
+	Reg. of cell prolif (-) (APOPTOSIS ?)	neg. regulation of cell proliferation, tumor suppress	RARRES3	retinoic acid receptor responder (tazarotene	1,00E-04
-	Reg. of cell prolif (+)	pos. regulation of cell proliferation	EGF	epidermal growth factor (beta-urogastrone)	0,009
+	Reg. of cell prolif (APOPTOSIS inhibitor)	apoptosis inhibitor	BIRC3	baculoviral IAP repeat-containing 3	0,0327
+	Reg. of cell prolif (APOPTOSIS)	cell cycle, JAK/STAT, caspase activation, transcri	STAT1	signal transducer and activator of transcripti	3,00E-04
+	Reg. of cell prolif (APOPTOSIS)	apoptosis, cell signaling	TNFSF10	tumor necrosis factor (ligand) superfamily, n	0,0021
-	Reg. of gene expression, DNA repair	transcription factor, represses activation	ATF3	activating transcription factor 3	0,0402
-	Reg. of gene expression, DNA repair	cell cycle, DNA repair	MRE11A	MRE11 meiotic recombination 11 homolog A	0,0482
+	Reg. of gene expression, DNA repair	cell cycle, mitosis	CDC25B	cell division cycle 25B	1,00E-04
+	Reg. of gene expression, DNA repair	response to stress, transcription factor	HIF1A	hypoxia-inducible factor 1, alpha subunit (bas	3,00E-04
+	Reg. of gene expression, DNA repair	RNA-processing	RBPMS	RNA-binding protein gene with multiple splici	0,0344
-	signal transduction	transmembrane receptor, signal transduction	EPHB1	**EphB1	3,00E-04
+	signal transduction	signal transducer, heat stable protein	CARHSP1	calcium regulated heat stable protein 1, 24kD	1,00E-04
+	signal transduction	neurogenesis, signal transduction	SMPD1	sphingomyelin phosphodiesterase 1, acid lys	0,0262
+	signal transduction	signal transduction, protein ER-retention	GRP58	**glucose regulated protein, 58kDa	1,00E-04
+	skeletal development	skeletal development	OSF-2	osteoblast specific factor 2 (fasciclin I-like)	0,012

Hauser P et al, Lab Invest

2004,84:353-61

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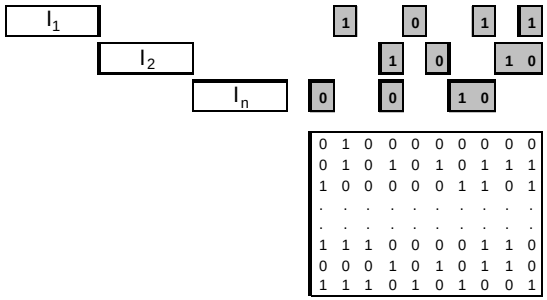
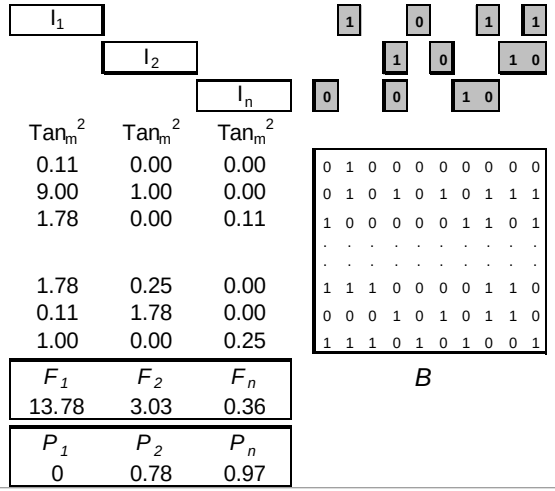
Genetic algorithm to derive joint promoter modules in coexpressed genes

$$B = \begin{pmatrix} b_{11} & \cdots & b_{1m} \\ \vdots & \ddots & \vdots \\ b_{g1} & \cdots & b_{gm} \end{pmatrix}$$

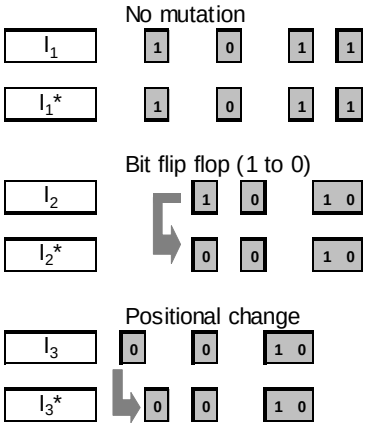
1. Generation of an initial population I



2. Evaluation of each single individual I_K of population I



3. Generation of a child population



4. Loop to step 2 until convergence criterion is met

Perco et al. Bioinformatics 2005

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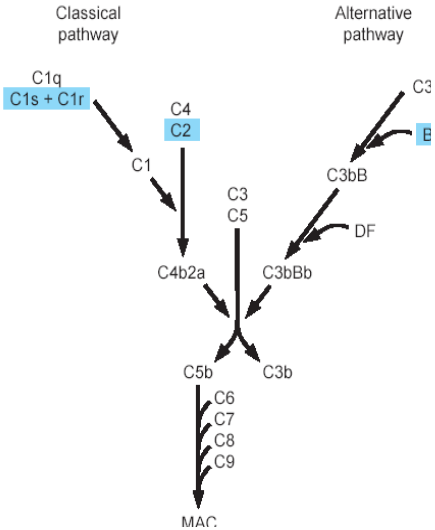
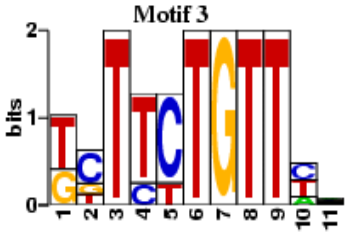
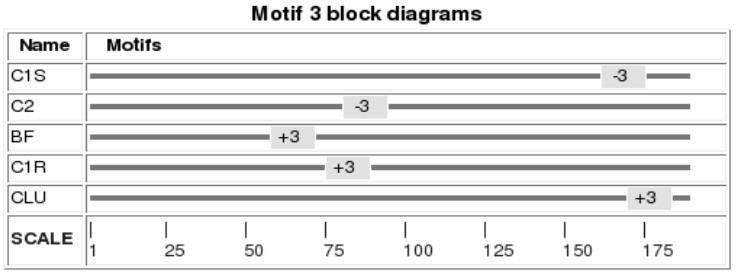
Joint promotor modules

Gene symbol	*Gene name*	*UniGene ID*	*Expression*	
			CAD	*LIV*
Complement system				
BF	B-factor, properdin	Hs.69771	2.57	−0.48
C1R	complement component 1, r subcomponent	Hs.1279	2.23	−0.54
C2	complement component 2	Hs.2253	0.31	−2.28
C1S	complement component 1, s subcomponent	Hs.169756	2.49	0.82
CLU	clusterin	Hs.75106	0.54	−0.91



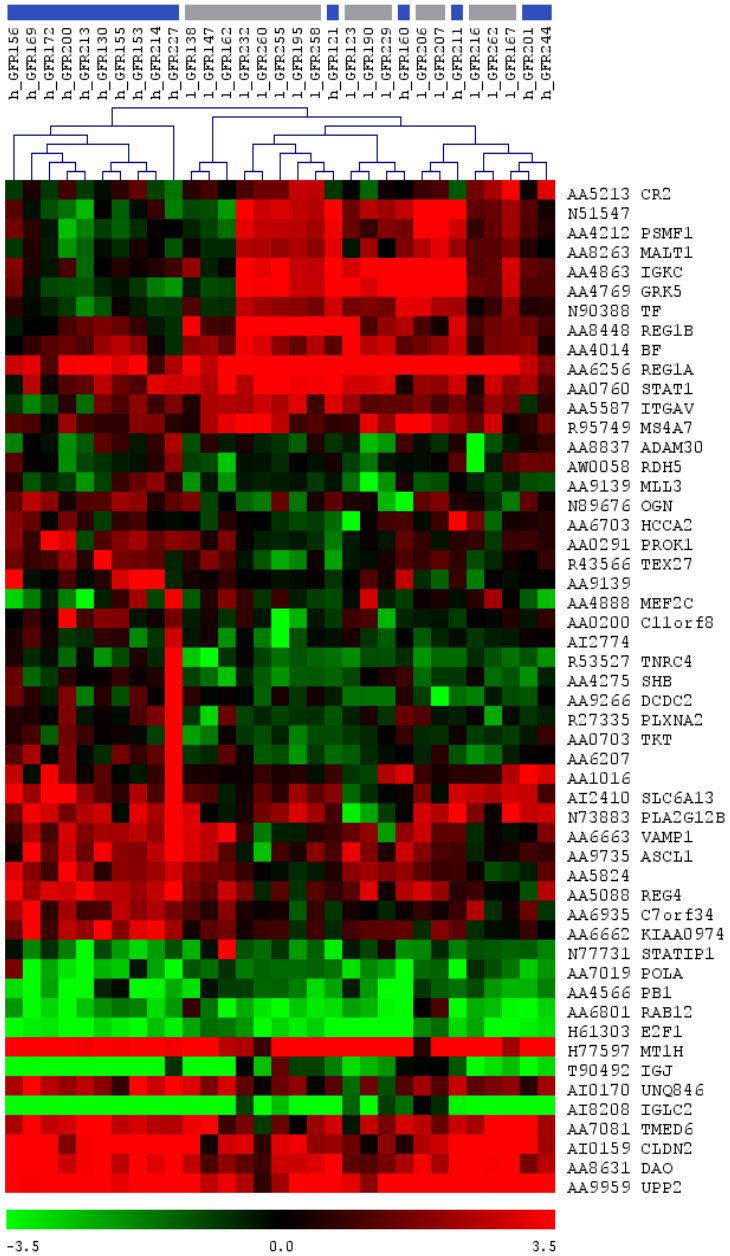




Kainz A et al. Am J Transplant 2004; 4:1595-1604

Perco et al. Bioinformatics 2005

Molecular Signature predicts 1yr graft function



R.O.56/33 **Kainz et al. Transplantation 2007, 83:1048-1054**

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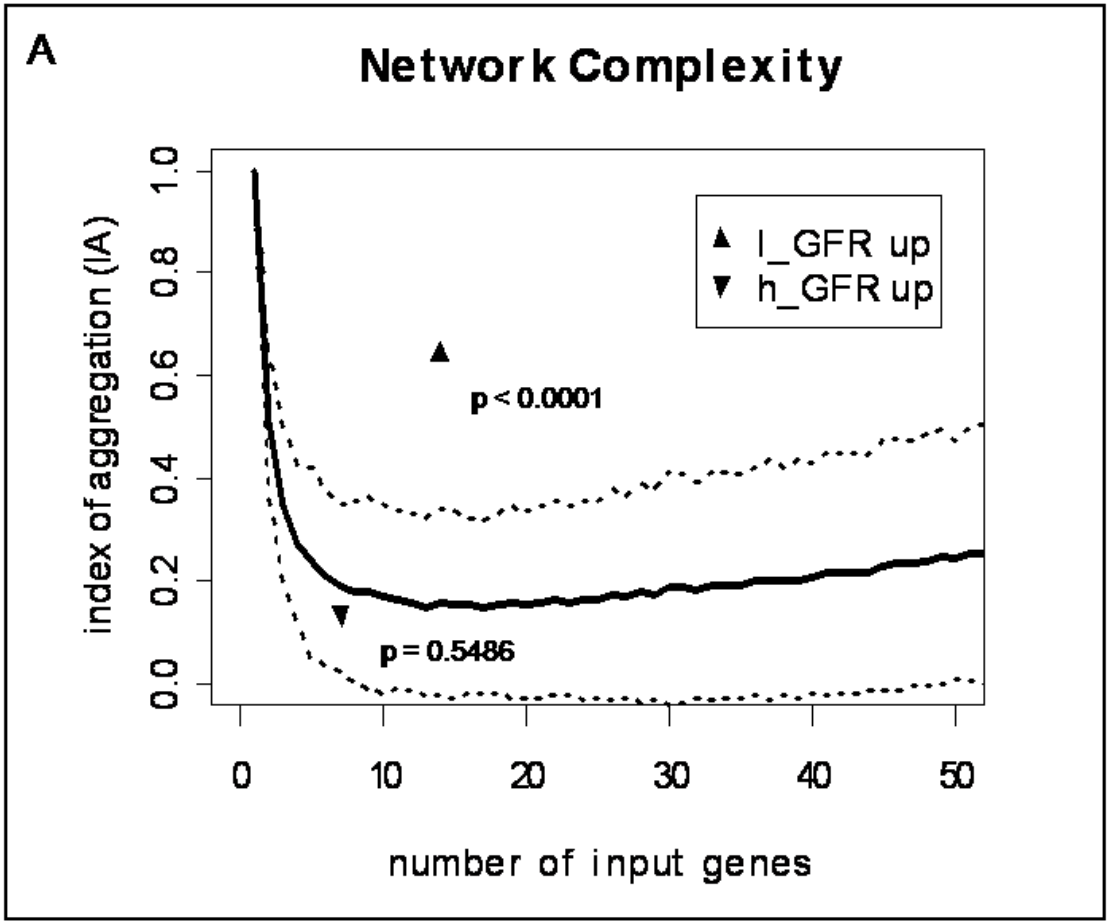
Protein-protein interaction networks of differentially regulated genes



Kainz et al. Transplantation 2007, 83:1048-1054

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Agenda

- SNP data
- Protein coding gene transcriptomics
- miRNA transcriptomics

What is ‚Omics‘?

- Neologism ‘omics’ informally refers to a field of study ending in -omics, such as genomics or proteomics.

- All constituents considered collectively

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Agenda

- Pharmacogenomics of Immunosuppressants
- GWAS and outcomes
- Functional Genomics (Biopsies, BCAR)
- Systems Biology in Transplantation

Biotransformation Enzymes and Drug Transporters Pharmacogenetics in Relation to Immunosuppressive Drugs: Impact on Pharmacokinetics and Clinical Outcome

Michel Mourad,[1,5] Pierre Wallemacq,[2] Martine De Meyer,[1] Jacques Malaise,[1] Luc De Pauw,[1] Djamila Chaïb Eddour,[1] Eric Goffin,[3] Jan Lerut,[1] and Vincent Haufroid[2,4]

Immunosuppressive drugs commonly used after organ transplantation to prevent acute rejection including tacrolimus, cyclosporine, sirolimus, and mycophenolic acid are characterized by a narrow therapeutic index and broad interindividual variability in their pharmacokinetics. Adequate immunosuppression aims to reach an optimal benefit–risk ratio. Therapeutic drug monitoring represents a crucial step in routine practice to maintain blood concentrations within the target window, because the bioavailability of these drugs depends on their absorption, distribution, biotransformation, and elimination. Single nucleotide polymorphisms (SNPs) in genes encoding biotransformation enzymes (CYP3A) and drug transporters (*ABCB1*) have opened up a promising way for the selection of individual dosages. The relationship of these SNPs with immunosuppressive drug pharmacokinetics was extensively studied after kidney, liver, heart, and lung transplantations. Patient susceptibility to nephrotoxicity in the long term was also reported in relation to some SNPs, which could allow effective assessment of individual risk and selection of treatment according to patient parameters. Further studies are needed to provide evidence that a genetic analysis combined with therapeutic drug monitoring has the potential to optimize drug use after transplantation.

Keywords: Pharmacogenetics, Pharmacokinetics, Immunosuppressive drugs, Renal function.

(*Transplantation* 2008;85: S19–S24)

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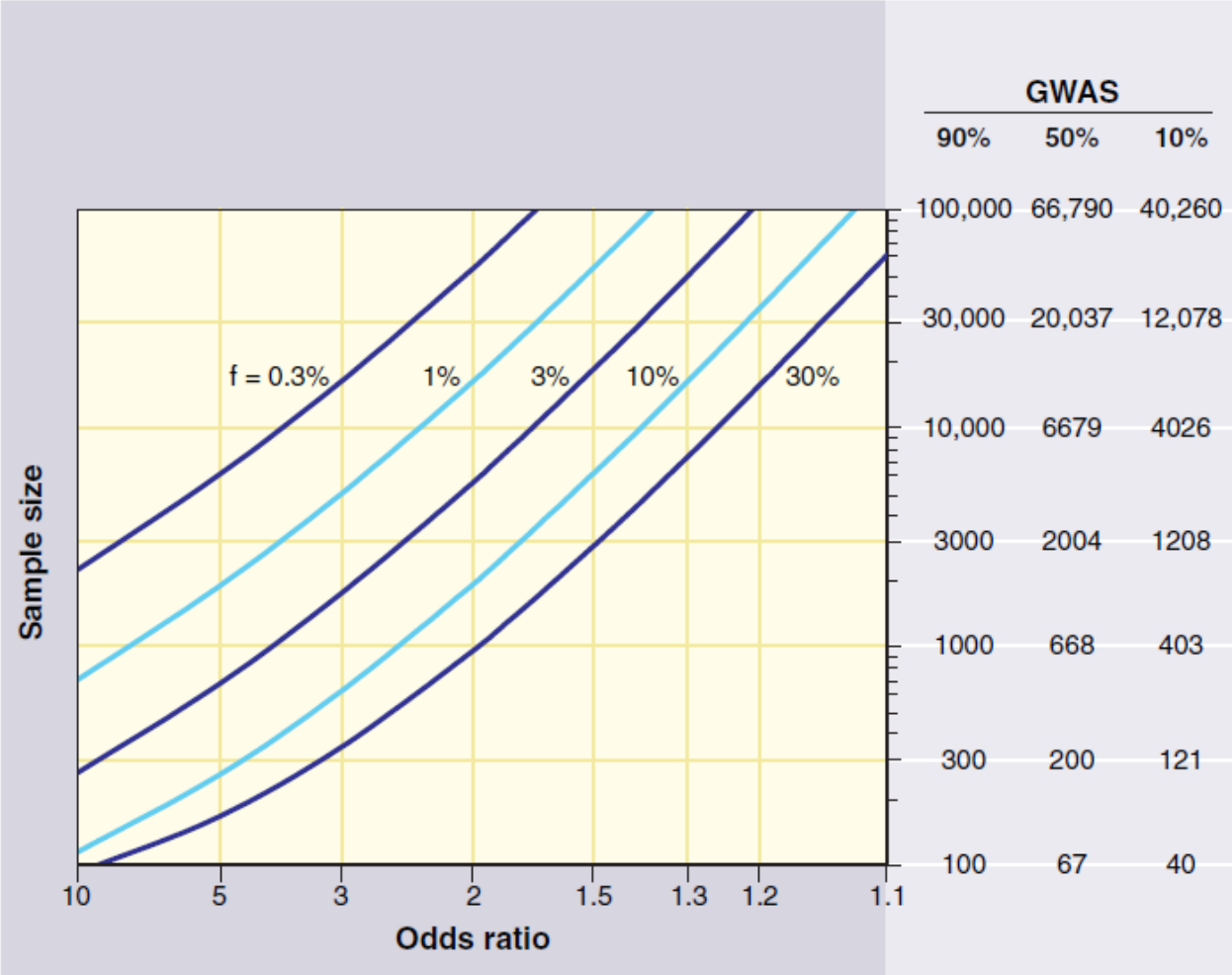
Agenda

- Pharmacogenomics of Immunosuppressants
- GWAS and outcomes
- Functional Genomics (Biopsies, BCAR)
- Systems Biology in Transplantation

Sample sizes required for genetic association studies



Altshuler D et al. Genetic Mapping in Human Disease. Science 322, 881 (2008)

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SNPs and outcomes after kidney transplantation

Table 1. Impact of *IL12B* 3′UTR Genotype on Graft Outcome in 253 Kidney Graft Recipients

Clinical Events	3′UTR Genotype		Odds Ratio (95% Confidence Interval)	*P*
	A/A (n = 141)	A/C and C/C (n = 112 [100 + 12])		
Graft survival (months)*	102 ± 4	99 ± 4	NA†	.768
Delayed graft function‡	30 (21%)	20 (18%)	0.80 (0.43–1.50)	.498
Acute rejection in the first year‡	36 (26%)	39 (35%)	1.56 (0.91–2.67)	.108
Positive CMV pp65 antigenemia‡	51 (36%)	56 (50%)	1.77 (1.07–2.92)	.027

*Graft survivals were expressed as mean values ± standard deviations by Kaplan-Meier life-table analysis and compared between 3′UTR genotypes by log-rank test.

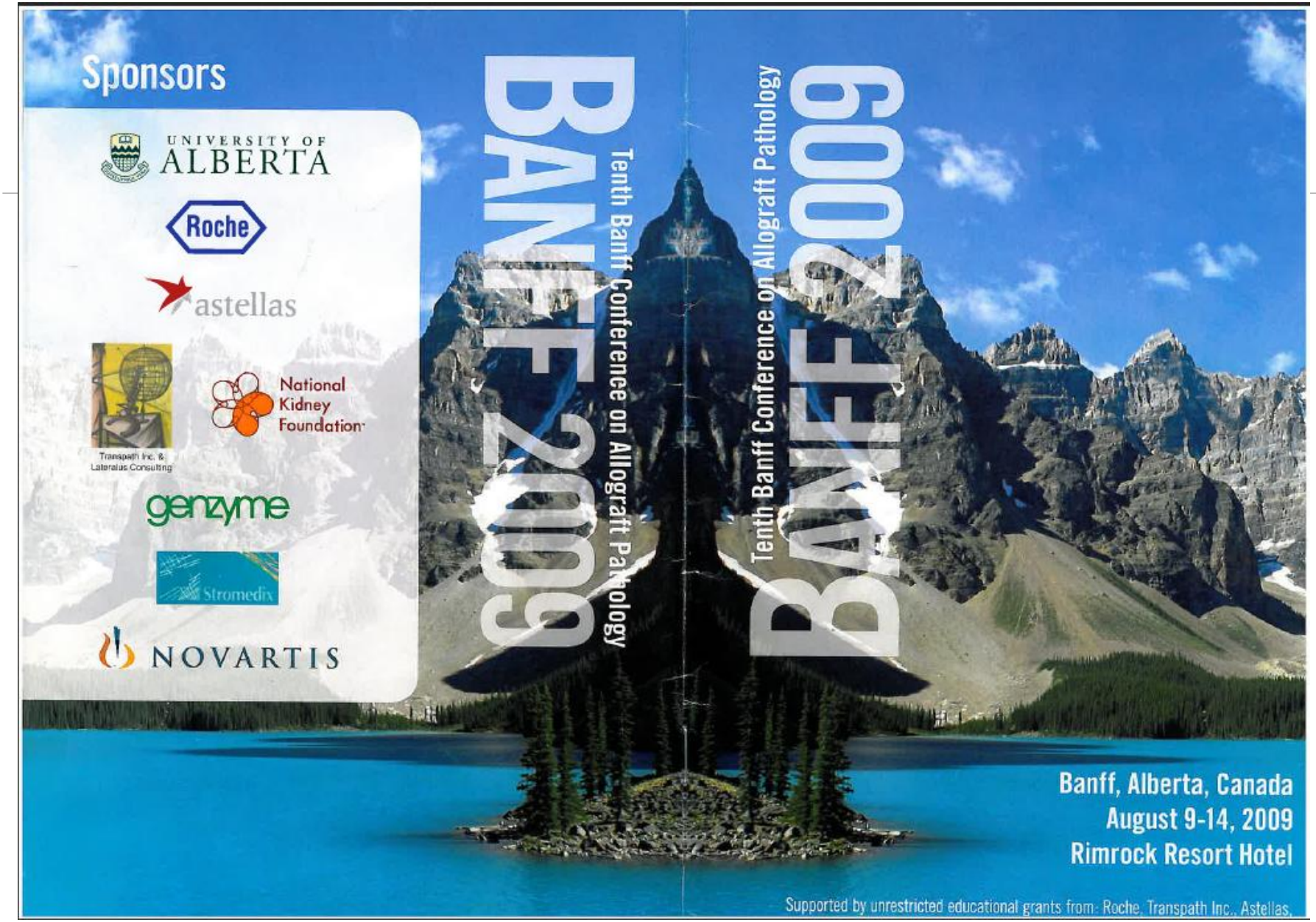
†Not applicable.

‡The occurrence of delayed graft function, acute rejection episodes, and CMV infections was compared between 3′UTR genotypes by chi-square test.

Hoffmann TW et al. Transplant Proc. 2009 Mar;41(2):654-6

Agenda

- Pharmacogenomics of Immunosuppressants
- GWAS and outcomes
- Functional Genomics (Biopsies, BCAR)
- Systems Biology in Transplantation



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Omics in Transplantation – Banff August 2009

	Concurrent Morning Session: Heart: Antibody mediated rejection in heart transplantation	***Rene Rodriguez, Adriana Zeevi***
8:00 - 8:05	**Heart:** Introduction and goals for the session	Rene Rodriguez, Adriana Zeevi
8:05 - 8:30	**Heart:** Gene expression in AMR - the Edmonton data from 100 microarrays of heart allograft biopsies	Banu Sis
8:00 - 8:30	**Plenary Session:** Non-invasive prediction of acute rejection in renal allografts	Manikkam Suthanthiran
8:30 - 9:00	**Plenary Session:** Genomics and outcomes after renal transplantation	Rainer Oberbauer
8:30 - 8:50	**Heart:** Markers of antibody mediated rejection and accommodation in heart transplantation	Rene Rodriguez
8:50 - 9:30	**Heart:** Antibodies and the cardiac allograft: types, temporal appearance and minimum follow-up data points to assess a trend. How to interpret in conjunction with the clinical and pathology team	Adriana Zeevi, Nancy Reinsmoen
9:00 - 9:30	**Plenary Session:** Allo-specific cells as non-invasive markers of rejection risk and immunosuppressive effect	Rakesh Sindhi
9:30 - 10:00	**Plenary Session:** Urine proteomics in chronic allograft dysfunction	Josep Campistol
9:30 - 9:50	**Heart:** Diagnosis of AMR - controversies and implications from the clinicians (medical –surgical) point of view	Boudi Kfoury
10:00 - 10:30	**Coffee Break**	
10:30 - 10:45	**Heart:** AMR Current Practice Survey - Europe	Margaret Burke, Annalisa Angelini
10:45 - 11:00	**Heart:** AMR Current Practice Survey - North America	Marc Halushka
10:30 - 11:00	**Plenary Session:** Non-invasive approaches to diagnosis in liver allografts	Hans Pratschke

FRIDAY 14 AUGUST 2009 (Day 5)

Time	Topic	Speaker
	Plenary Session: Summary of organ sessions	***Mark Haas, Bob Colvin***
7:30 - 8:00	Kidney	Lorraine Racusen
8:00 - 8:10	BKN consensus classification summary	Volker Nickeleit
8:10 - 8:40	Pancreas	Cinthia Drachenberg
8:40 - 9:10	Heart	Rene Rodriguez
9:10 - 9:40	Liver	Jake Demetris
9:40 - 10:10	Composite Tissue	Linda Cendales
10:00 - 10:30	**Coffee Break**	
10:30 - 11:00	Omics Technologies	Phil Halloran
11:00 - 11:30	Virtual microscopy as a tool for QA in transplantation pathology: report of a Banff working group	Mark Haas, Banu Sis
11:30 - 12:00	**Key Note Lecture** - "The Banff classification for allograft pathology: where we started, where we are now, where we will go"	Phil Halloran
12:00 - 1:00	**Lunch at Rimrock Resort Hotel**	
1:30	Bus departs for Banff Centre	Location: Meet in Rimrock Lobby
2:15 - 2:30	Tour of the first Banff Conference location	
2:30 - 3:00	**"Nutri-Break" Snack Break**	Location: Max Bell Central Foyer
	Session: Telepathology	***Jake Demetris***
3:00 - 3:30	Digital pathology: problems, promises and application to transplantation	Jake Demetris

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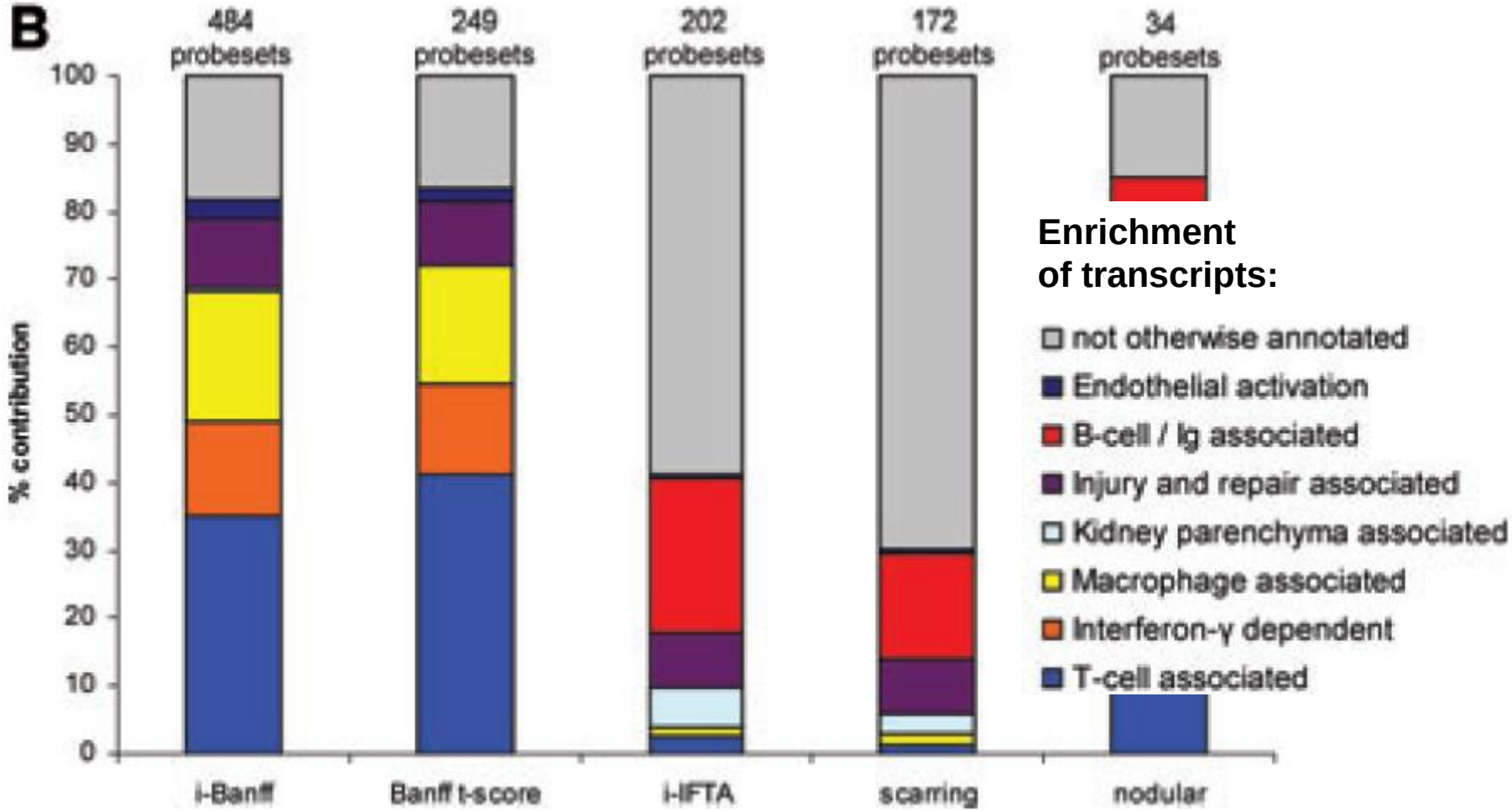
Correlations between individual genes and histological lesions and their overlap (n=129)



Mengel M et al. Am J Transplant. 2009 Jan;9(1):169-78.

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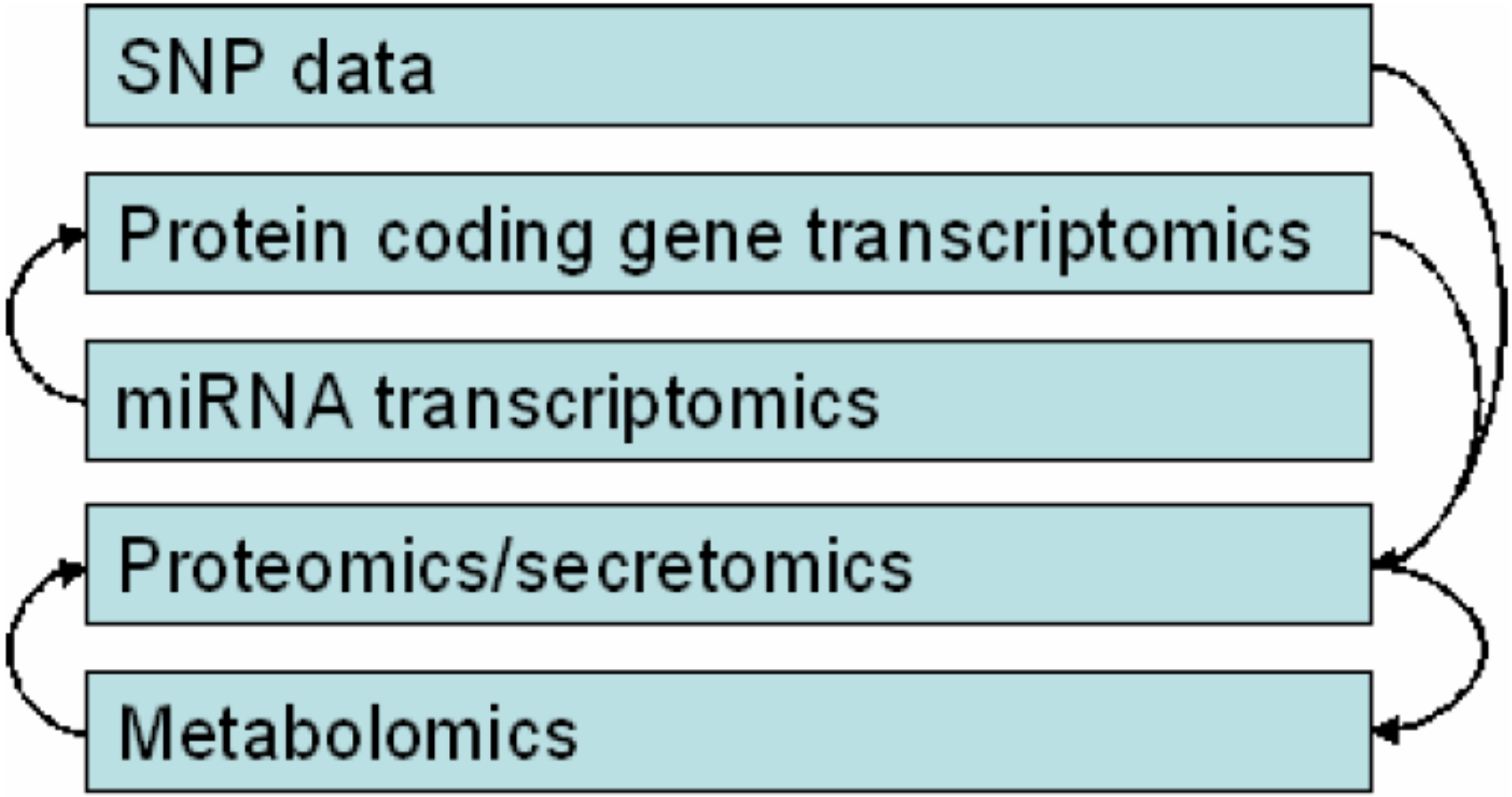
SysKID - Approach

SysKid
Collaborative Project
Systems Biology towards Novel Chronic Kidney Disease Diagnosis and Treatment



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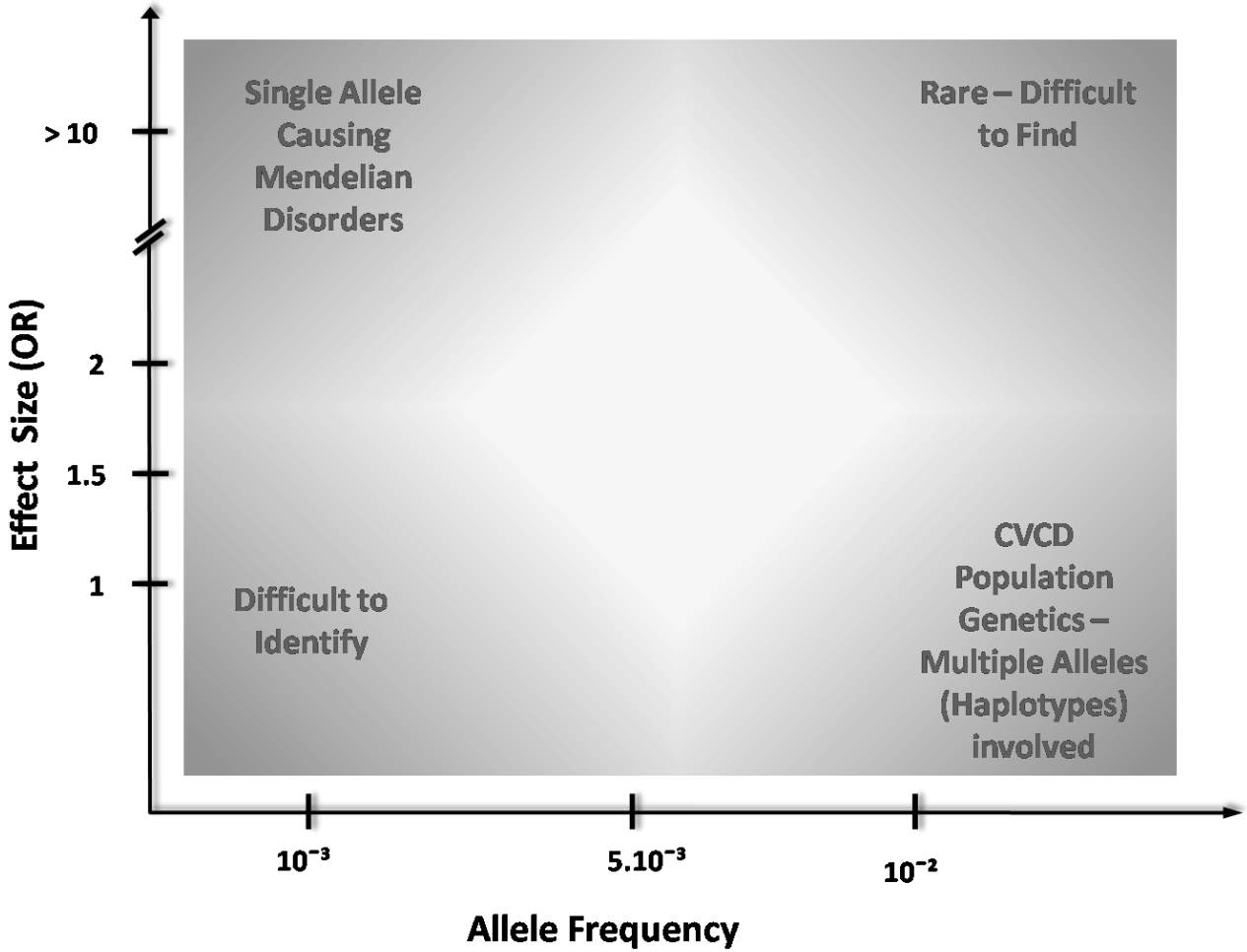
Genetic Analysis of SNPs



 Y Li, D Shiffman and R Oberbauer. In Bioinformatics for Omics Data: 2010 (in press)

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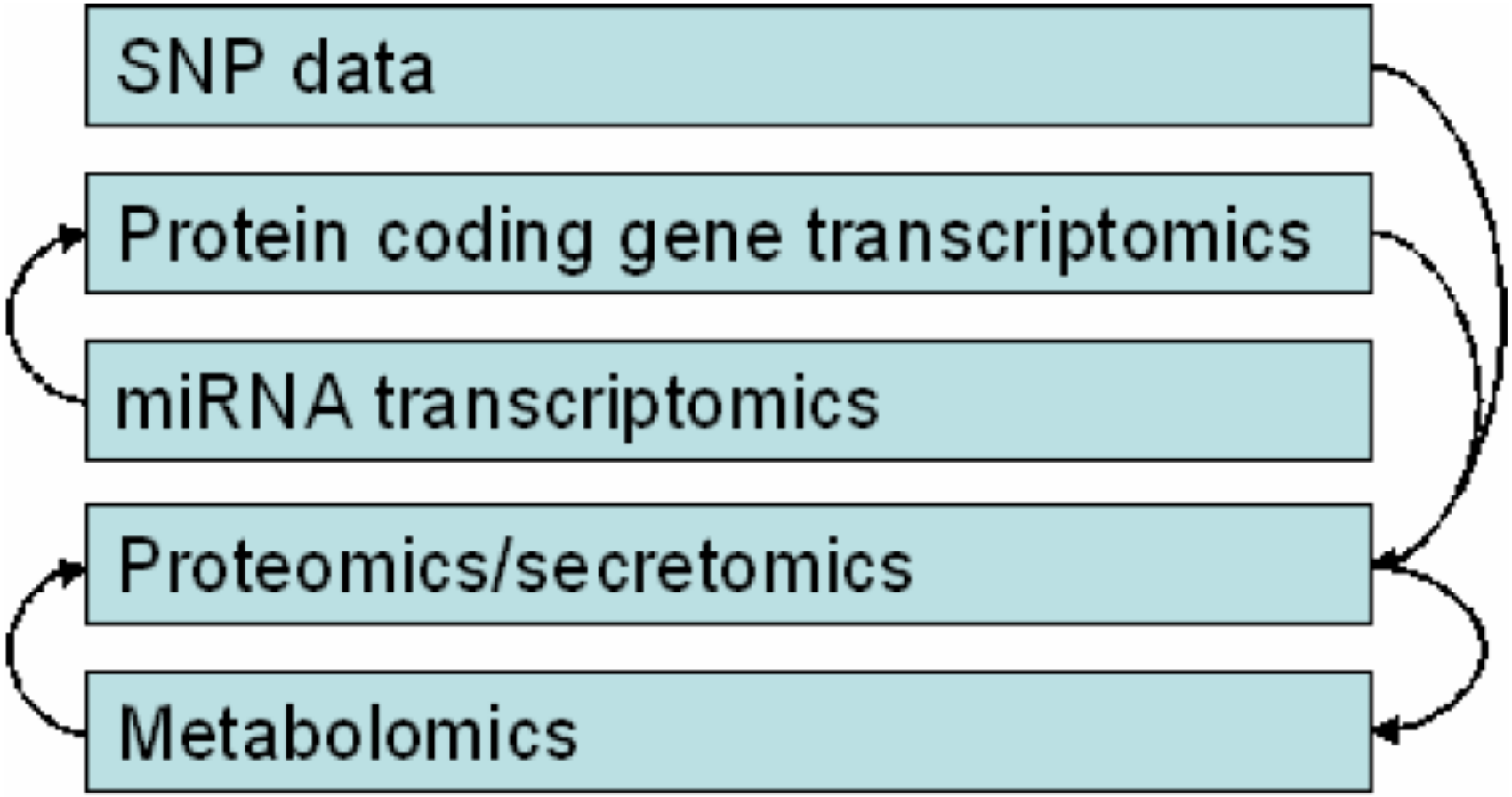
SysKID - Approach



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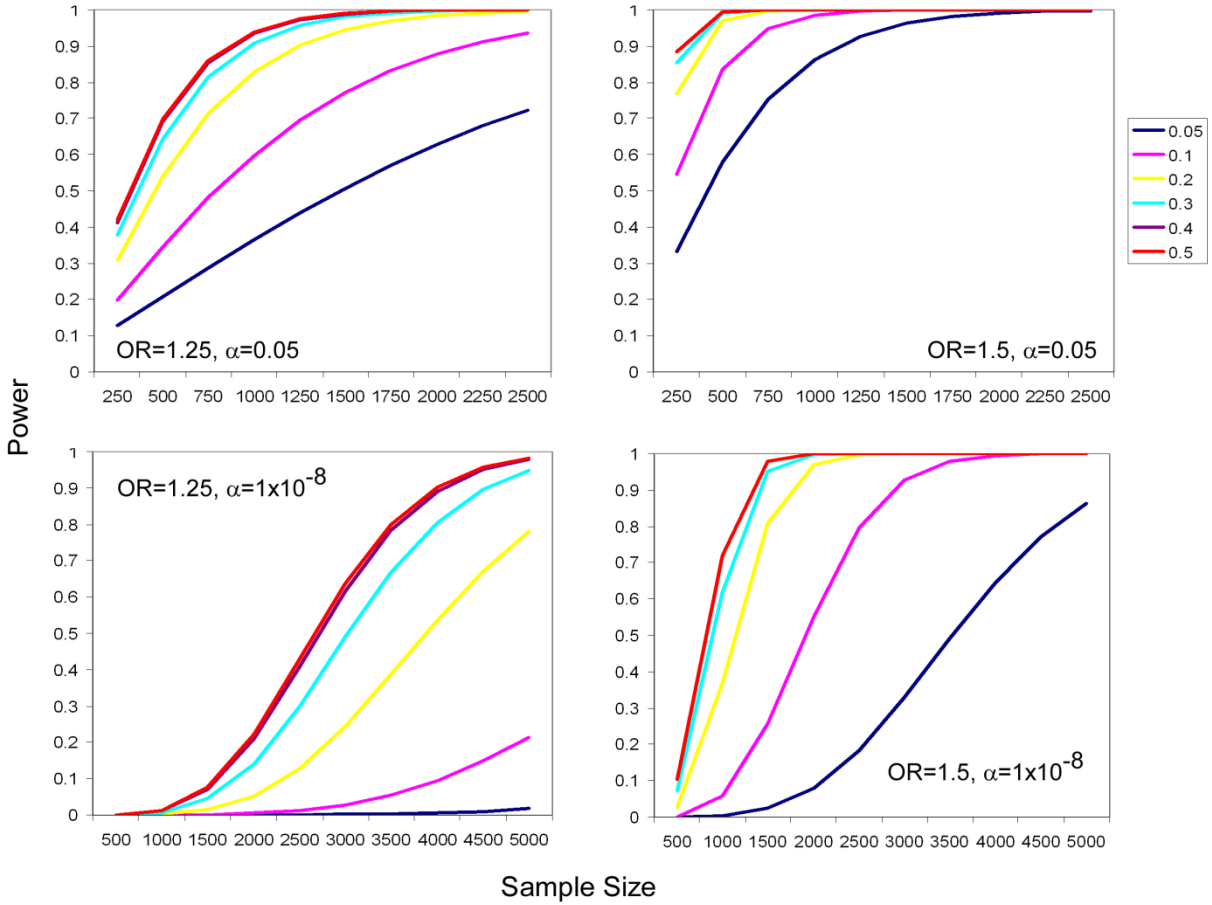
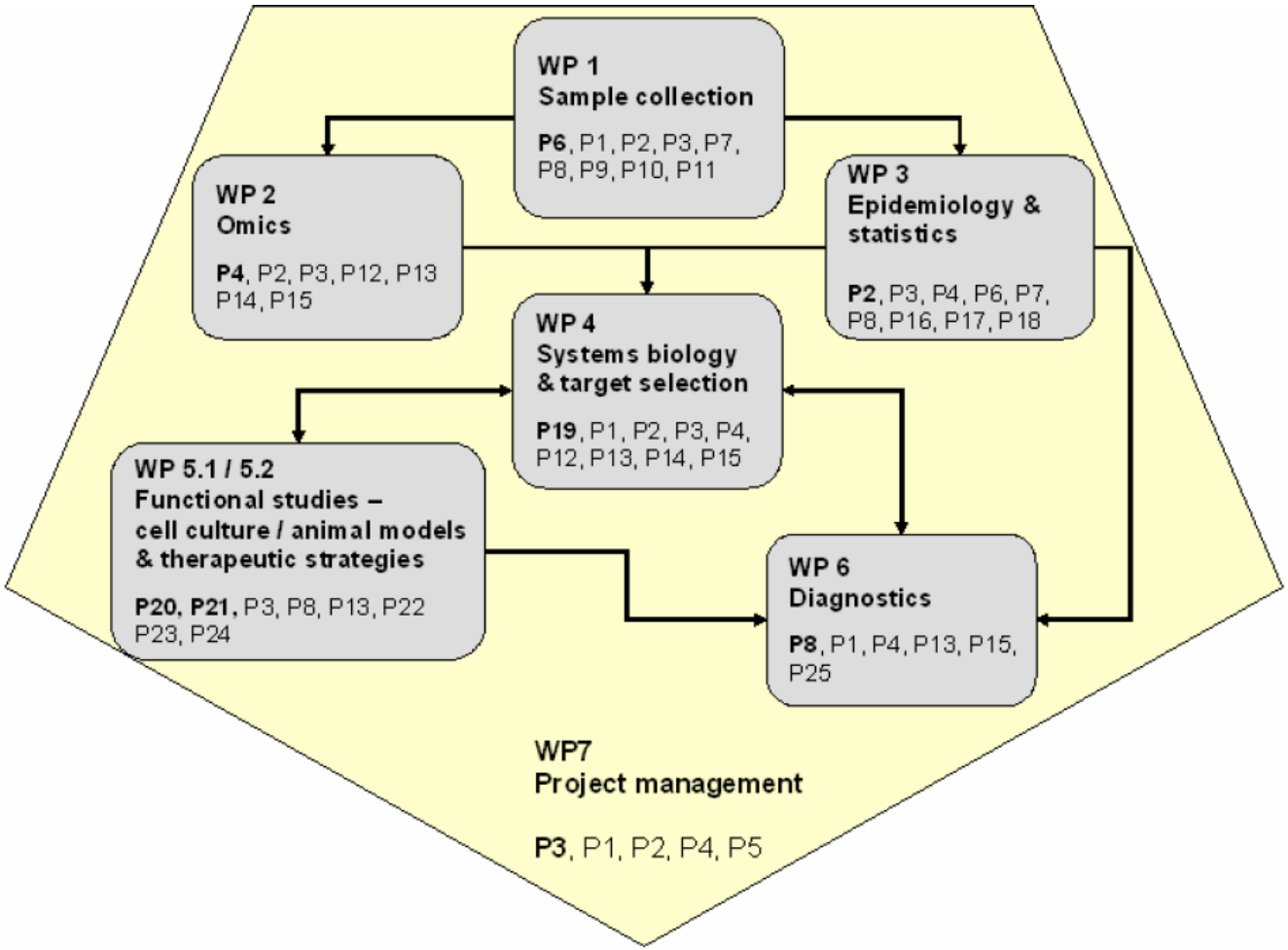
Power analysis of genome wide case-control studies



Lee, Y, Shiffman D, Oberabuer R. MMB 2010 (in press)

SysKID - schematic view of WP interdependency and involved partners

SysKid
Collaborative Project
Systems Biology towards Novel Chronic Kidney Disease Diagnosis and Treatment



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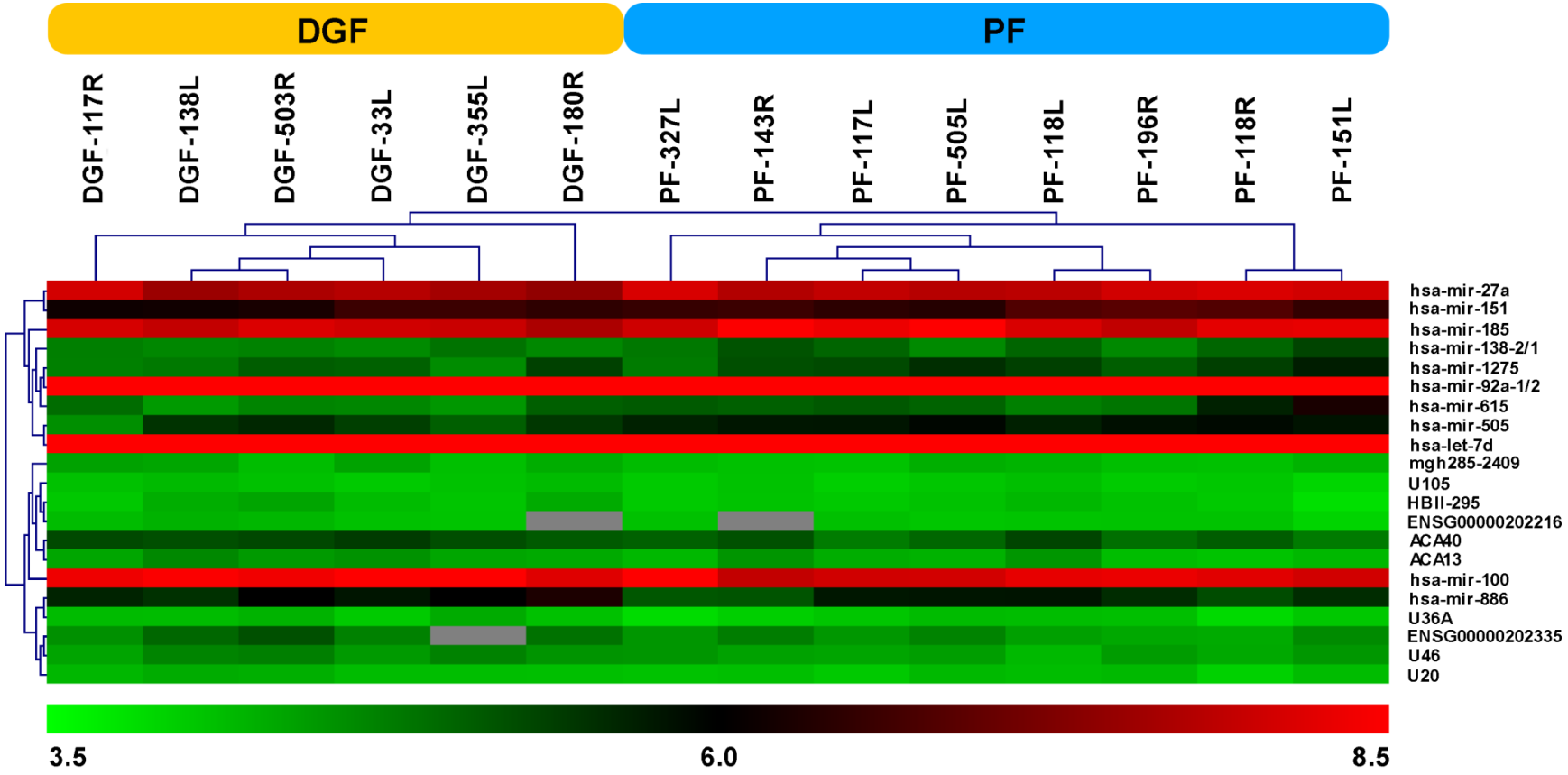
Differential regulation of miRNAs in delayed graft function – several target genes (miRANDA)



Wilflingseder J et al. 2010

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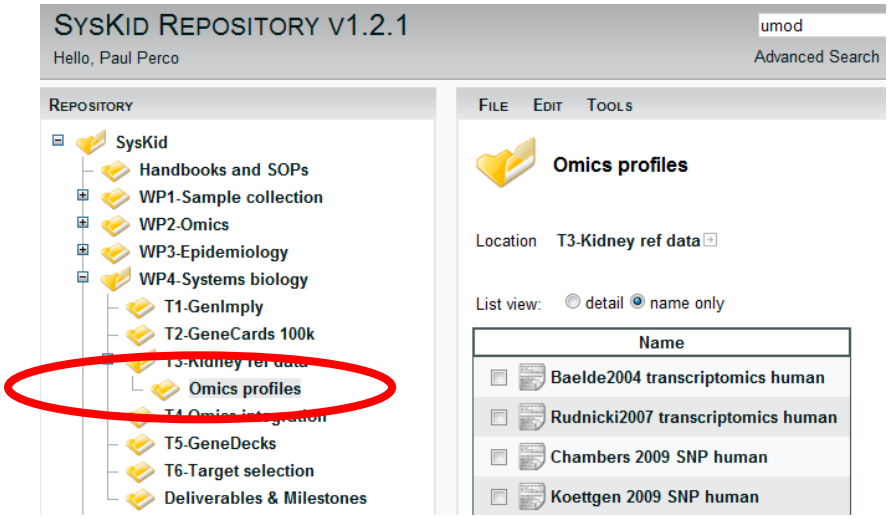
SysKid biomarkers – Omics sources

	human	animal models	cell culture
transcriptomics	4	6	2
proteomics	7	2	1
miRNAs	1	1	1
metabolomics	2	-	-
SNPs	4	-	-

Background coming from the partners (human, WP2, as well as models, WP5)

Public domain Omics profiles focused on DN

Foreground coming from the partners (human, WP2, as well as models, WP5)



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SysKid – Biomarker status

Document with the annotation of the 32 biomarker candidates

Annotation of reported biomarker candidates: SysKid00109

Core parameters	Annotation	Product info	SysKid info
marker name	literature	rec. protein	mol background
symbol	GO terms	antibodies	hypothesis
gene ID	pathways	primers	IPR
partner	diseases	assays	study results

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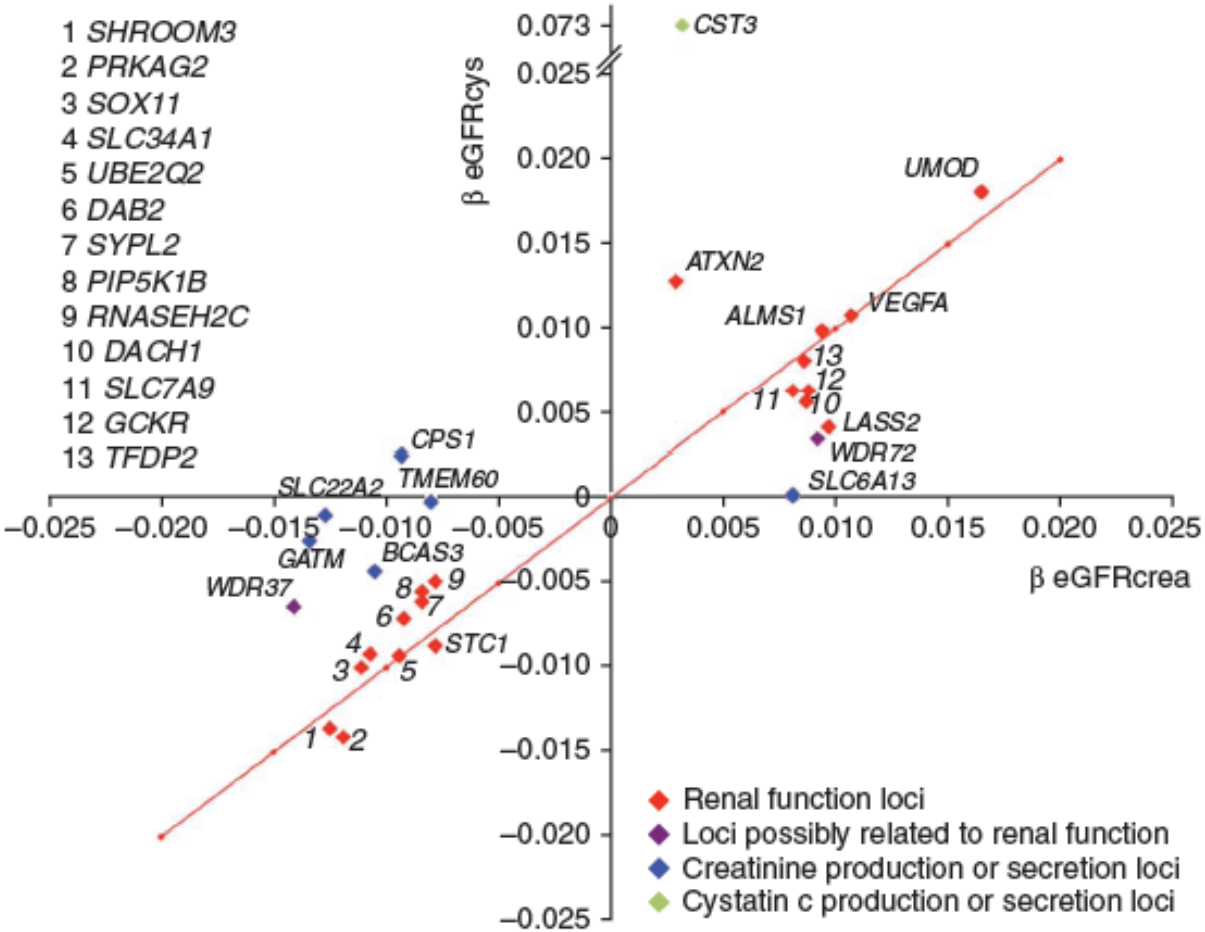
GWAS and eGFR estimated from serum creatinine and cystatin c



Kottgen A et al. Nat Genet. 2010 May;42(5):376-84

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Large scale EU Project - €16 Mio 2010-2015

SysKid
Collaborative Project
Systems Biology towards Novel Chronic Kidney Disease Diagnosis and Treatment

Project Number [1]	241544	Project Acronym [2]	SysKID

One form per project

General information

Project title [3]	Systems biology towards novel chronic kidney disease diagnosis and treatment *		
Starting date [4]	01/01/2010		
Duration in months [5]	60		
Call (part) identifier [6]	FP7-HEALTH-2009-single-stage		
Activity code(s) most relevant to your topic [7]	HEALTH-2009-2.4.5-2: Cellular and molecular mechanisms of the development of chronic kidney disease (CKD)		
Free keywords [8]	chronic kidney disease, diabetic nephropathy, diagnostic assays, therapy regimes, omics experiments, systems biology, functional genomics, patient outcome, clinical data repositories		

* Focus on diabetes and hypertension as the major drivers of CKD

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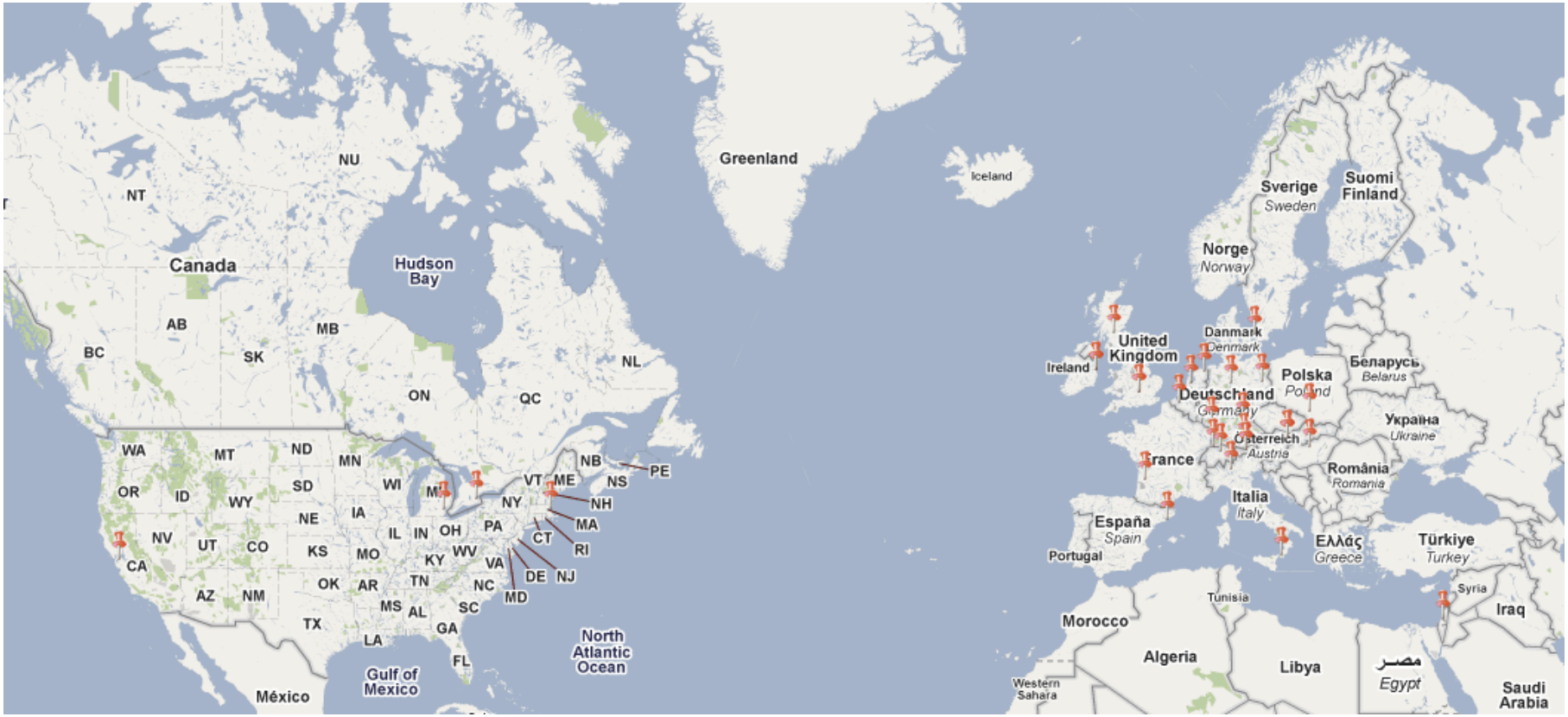
25 SysKid Partners

SysKid
Collaborative Project
Systems Biology towards Novel Chronic Kidney Disease Diagnosis and Treatment



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What is SysKid?

DM II

CKD

normo -> micro

micro -> marcoalbuminuria

biopsies

blood

serum

urine

clinical data

- SNPs, DNA
- Transcriptomics, mRNA
- Transcriptomics, miRNA
- Proteomics,
- Metabolomics

Computational Systems Biology

In-vitro models
In-vivo models

= SysKid Collaborative Project
Systems Biology towards Novel Chronic Kidney Disease Diagnosis and Treatment

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What is SysKid?

Applied Clinical Research

Epidemiology and Systems Biology

SysKid
Collaborative Project
Systems Biology towards Novel Chronic Kidney Disease Diagnosis and Treatment

Molecular Research

Development Partners

SysKid – Biomarker shortlist proposed

Symbol	Name
LCN2 (NGAL)	Lipocalin 2
FGF23	Fibroblast growth factor 23
SERPINE1 (PAI-1)	Serpine peptidase inhibitor, clade E, member 1
VCAN (CSPG2)	Versican
CTGF	Connective tissue growth factor
CCL2 (MCP-1)	Chemokine ligand 2
APOA1	Apolipoprotein A1

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