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Allgemein öffentliches Krankenhaus
Elisabethinen Linz

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

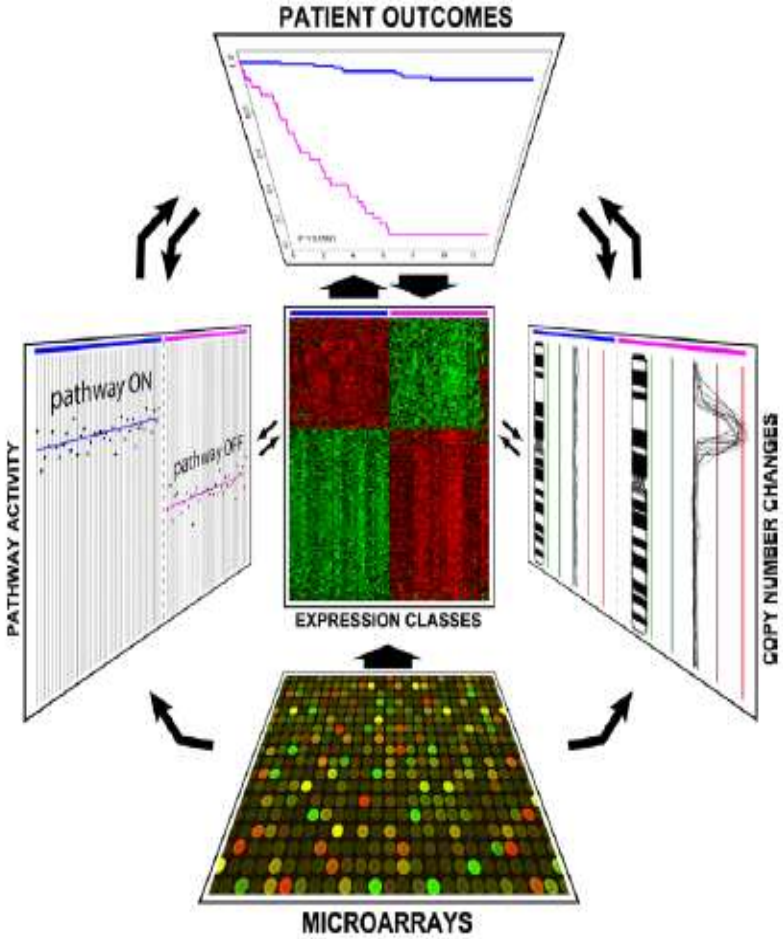
Rainer Oberbauer

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.

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 ...

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1866: Gregor Mendel discovers the laws of inheritan

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

2003: The Human Genon

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?

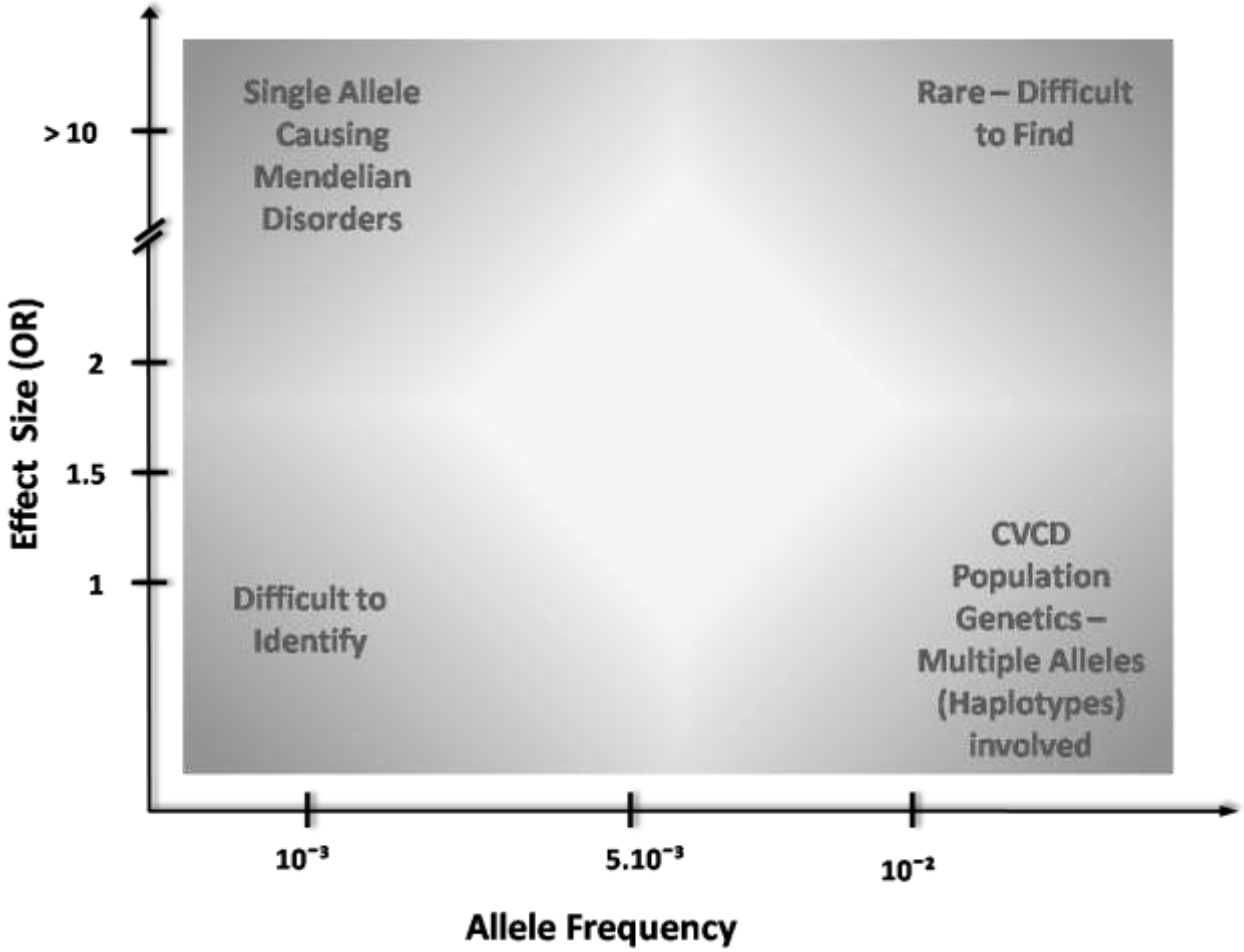
Family Inheritance

Do you have your mother's sense of taste?

Genome Labs

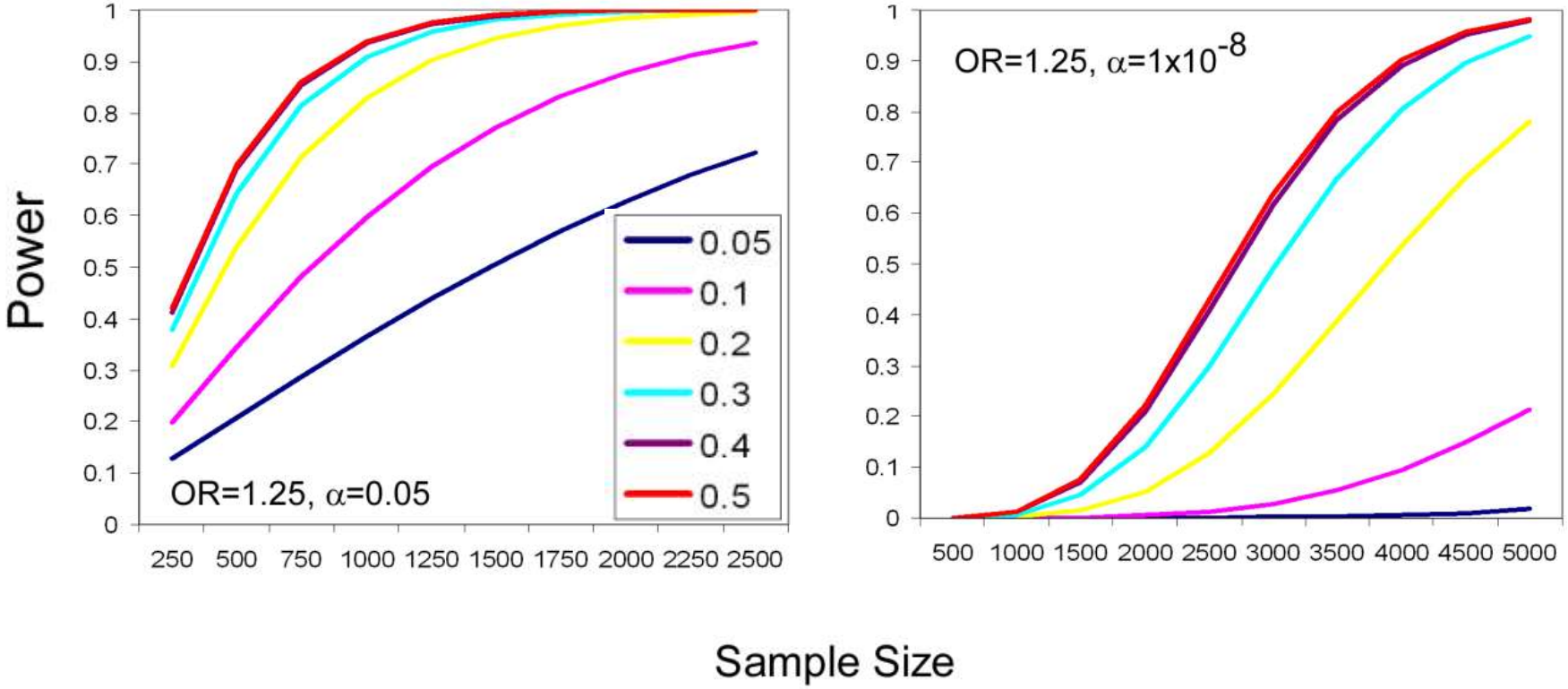
Would you like to search your genome?

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



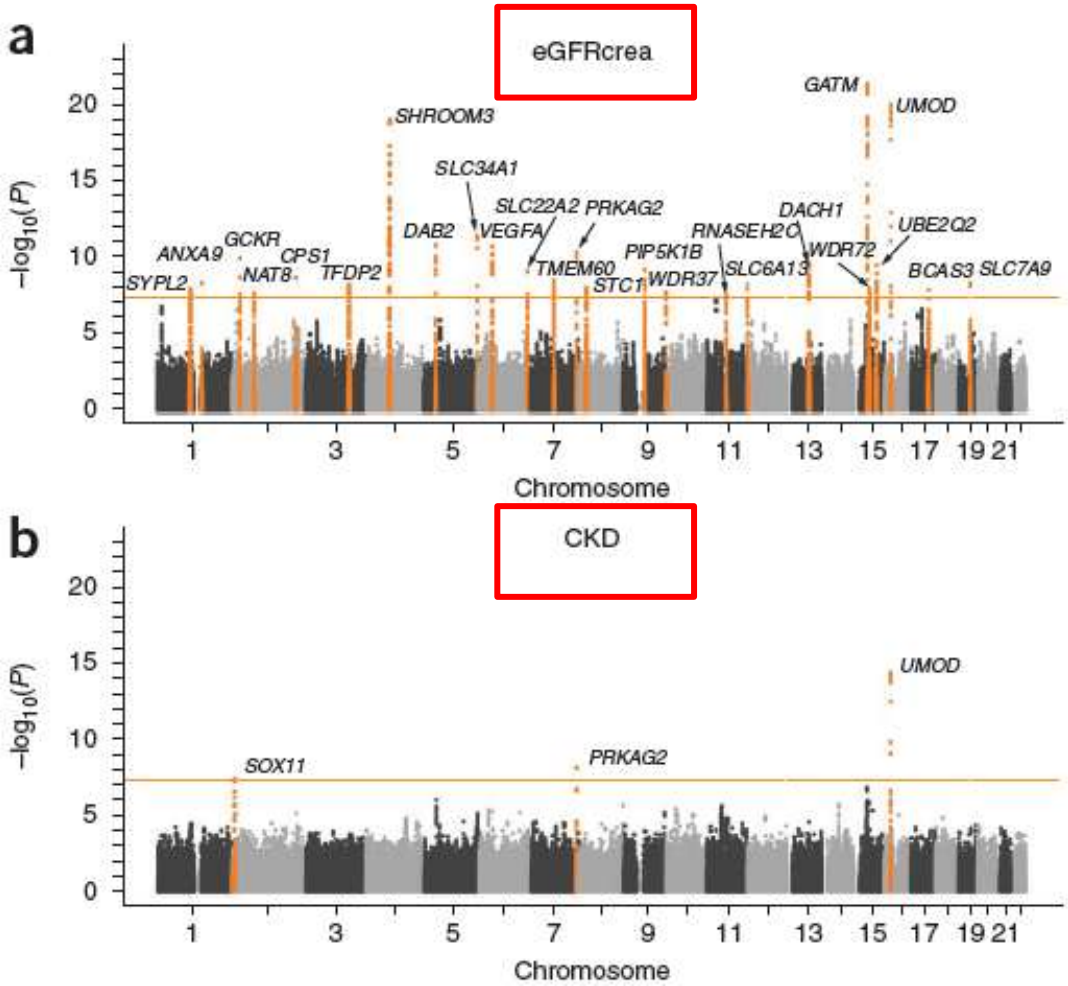
Le, Y, Shiffman D, Oberbauer R. MMB 2010 (in press)

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

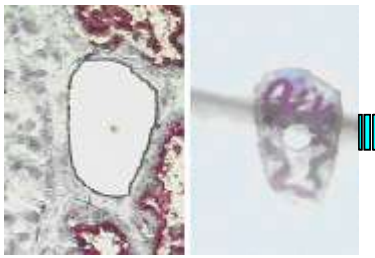
Systems biology of kidney injury

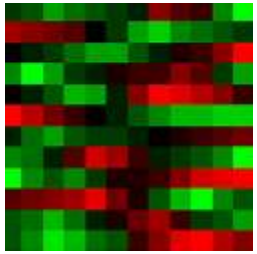
Laser Capture
Microdissection
Of Donor Kidneys

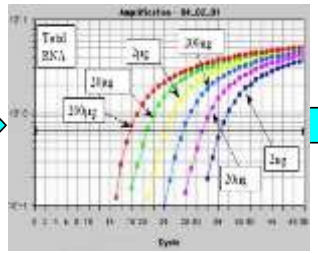
DNA
Microarrays

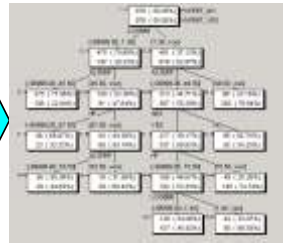
Quantitative
PCR

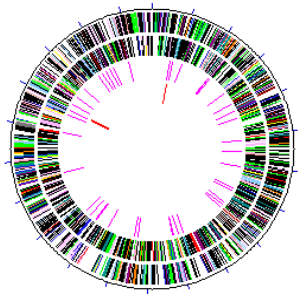
Data
Mining

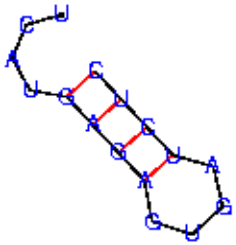


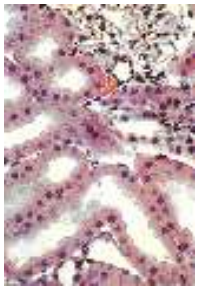


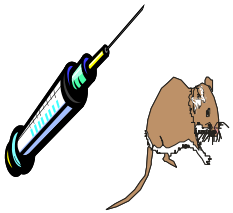












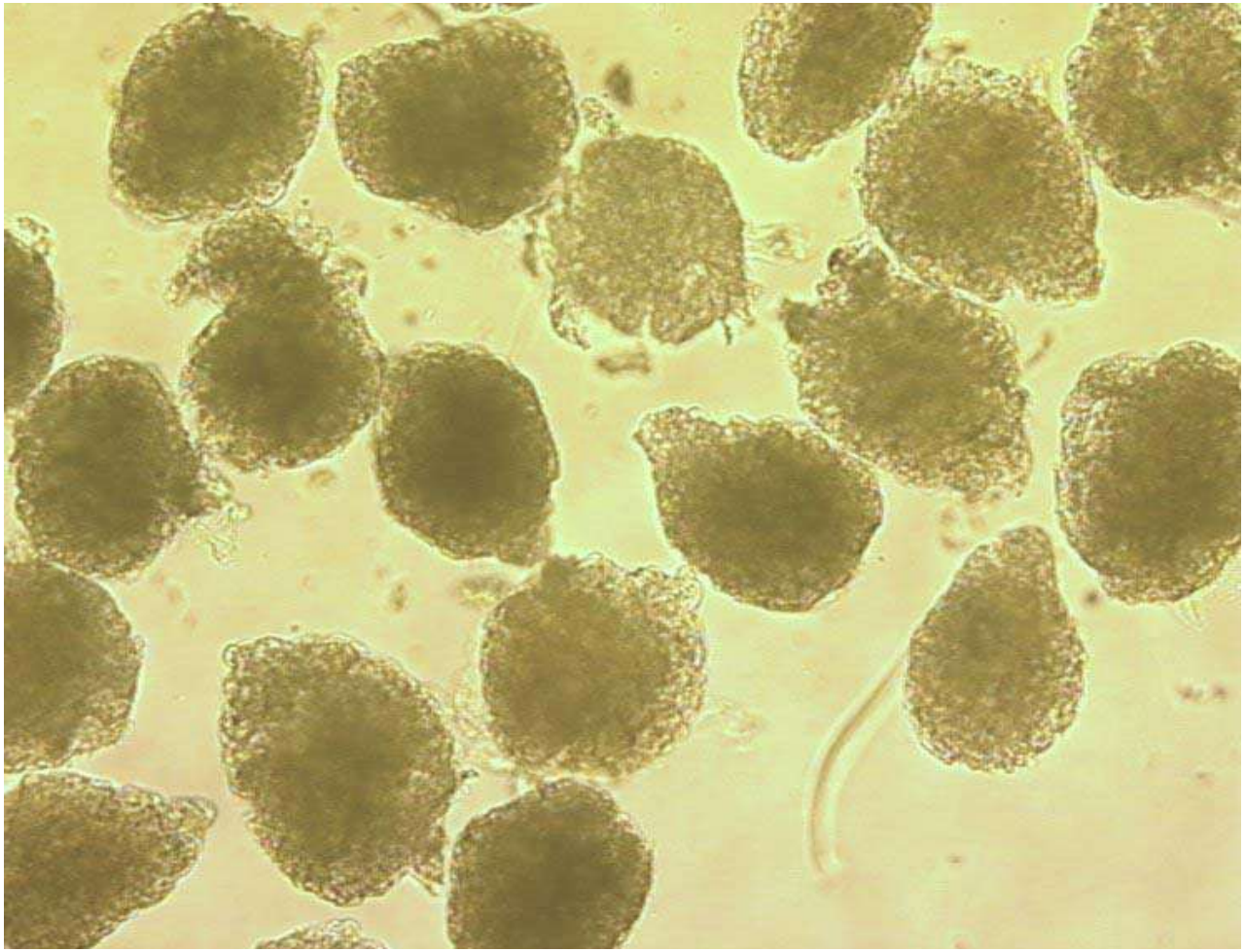
Target Gen
Definition

Antisense
Nucleotide
Design &
Synthese

In vitro
POC

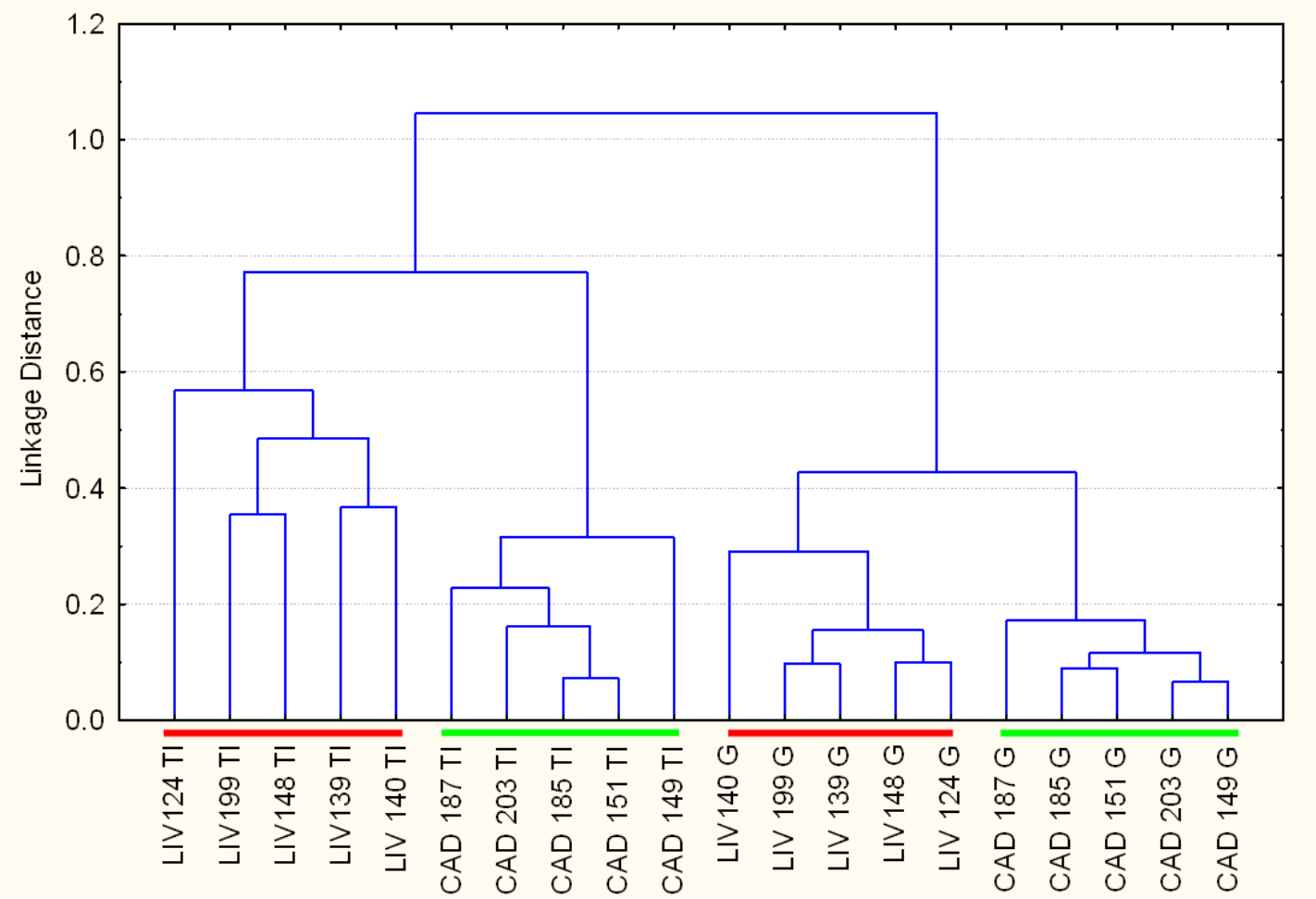
In vivo
POC

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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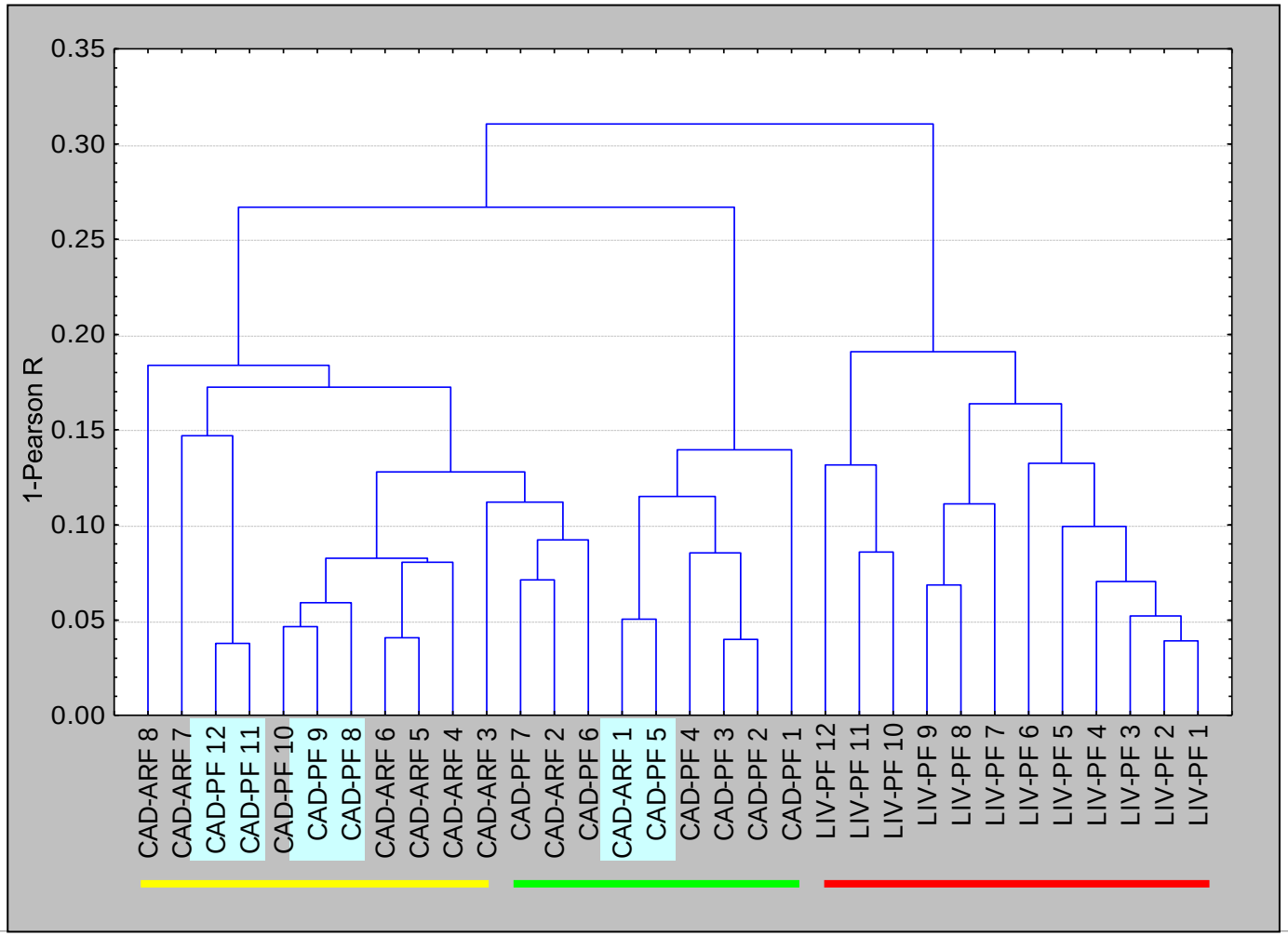
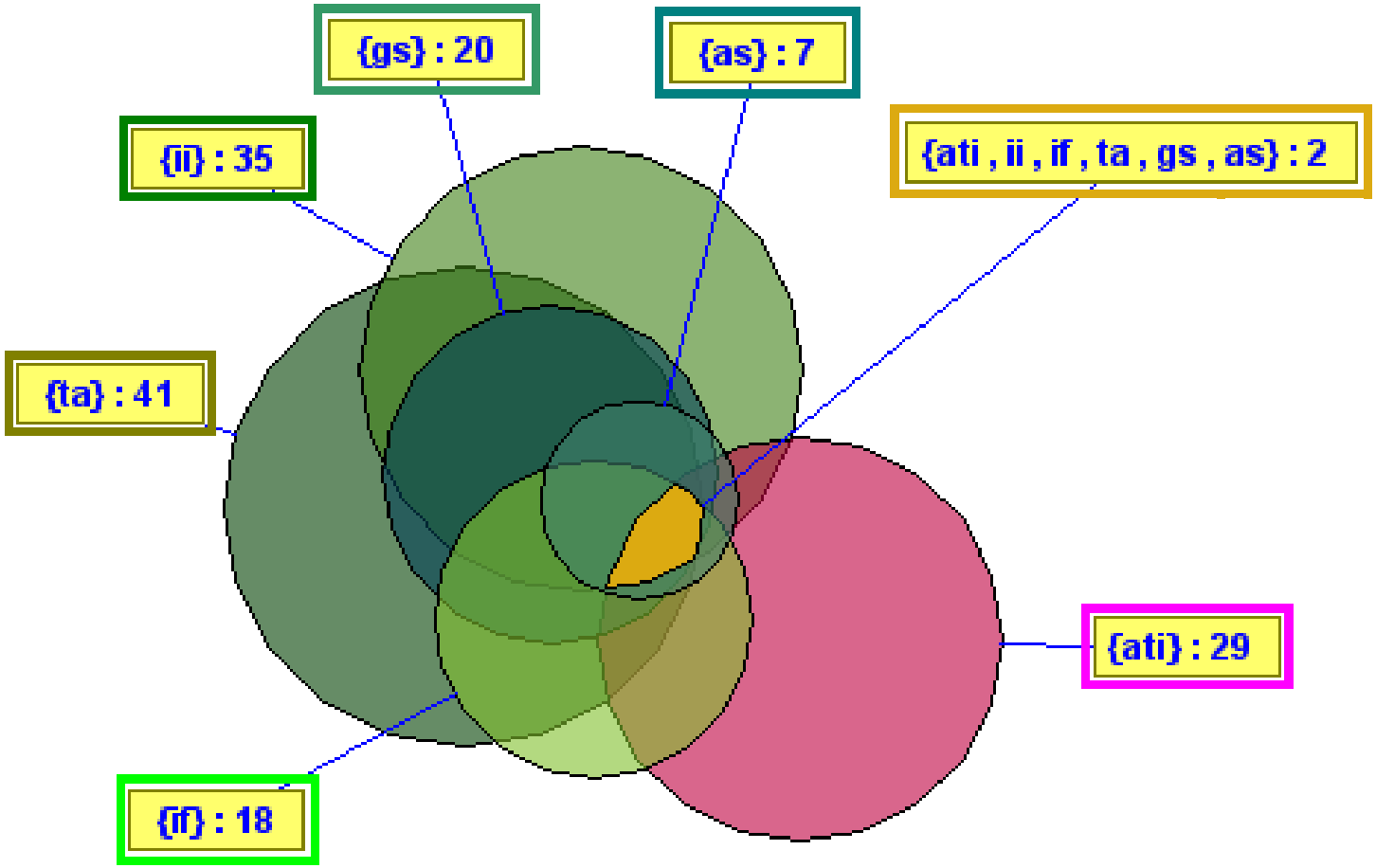
Unsupervised Cluster Analysis of Donor Kidney Biopsies



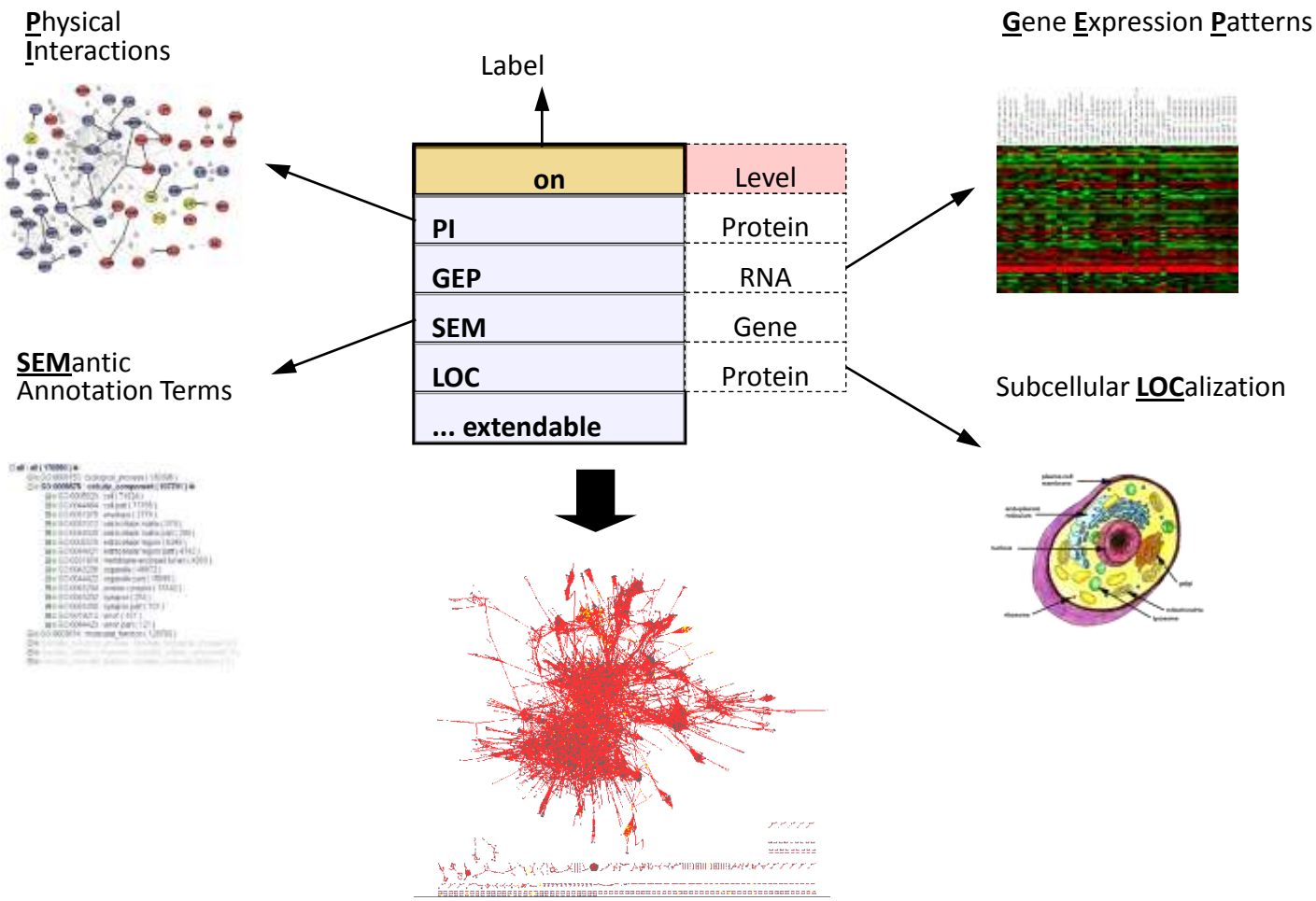
Hauser P et al, Lab Invest *2004, 84:353-61*

Histogenomics of deceased donor kidneys (n=82)



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

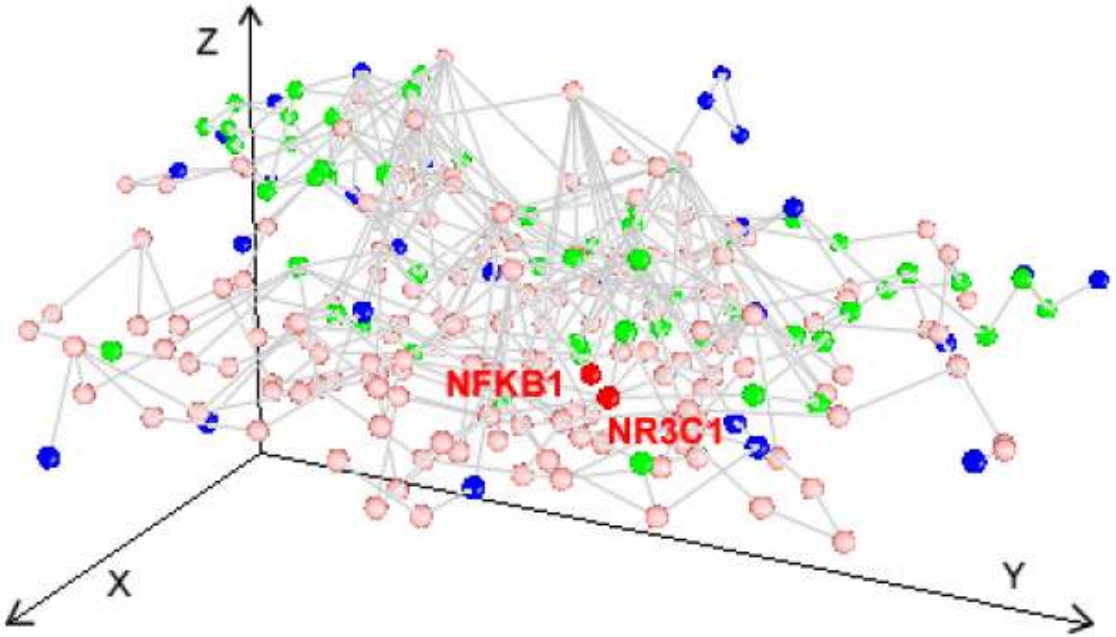
Systems Biology and omicsNET



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

omicsNET – Example – IRI/ARF

Inflammation networks in cadaveric donor organs



Inflammation/immunity/defense

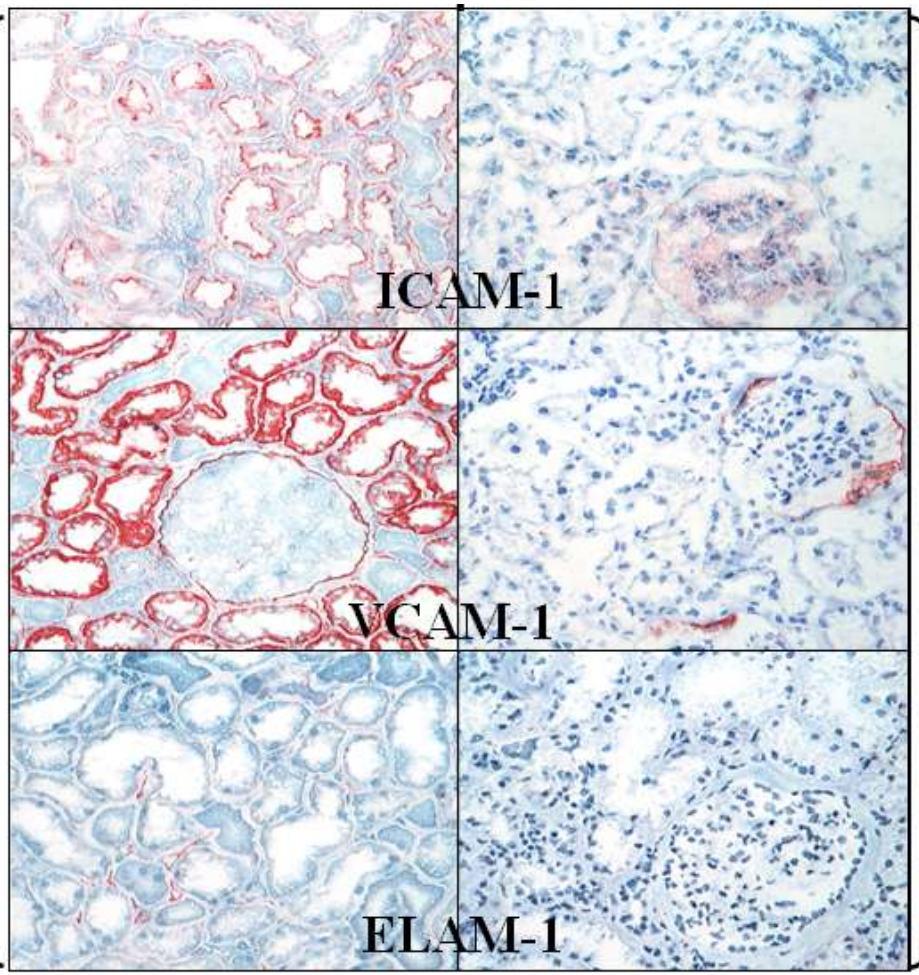
differentially regulated

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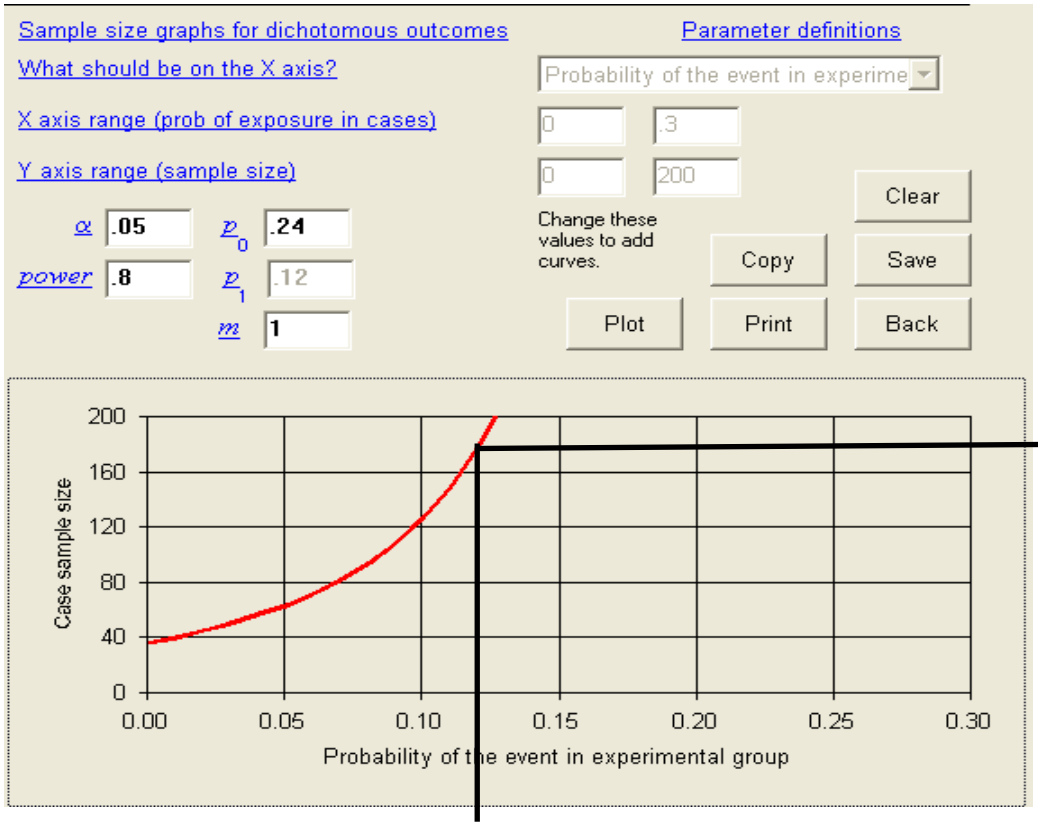
A Multicenter Double-Blinded RCT of Deceased Organ Donor Pre-Treatment with Corticosteroids for the Prevention of Postischemic Acute Renal Allograft Failure

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

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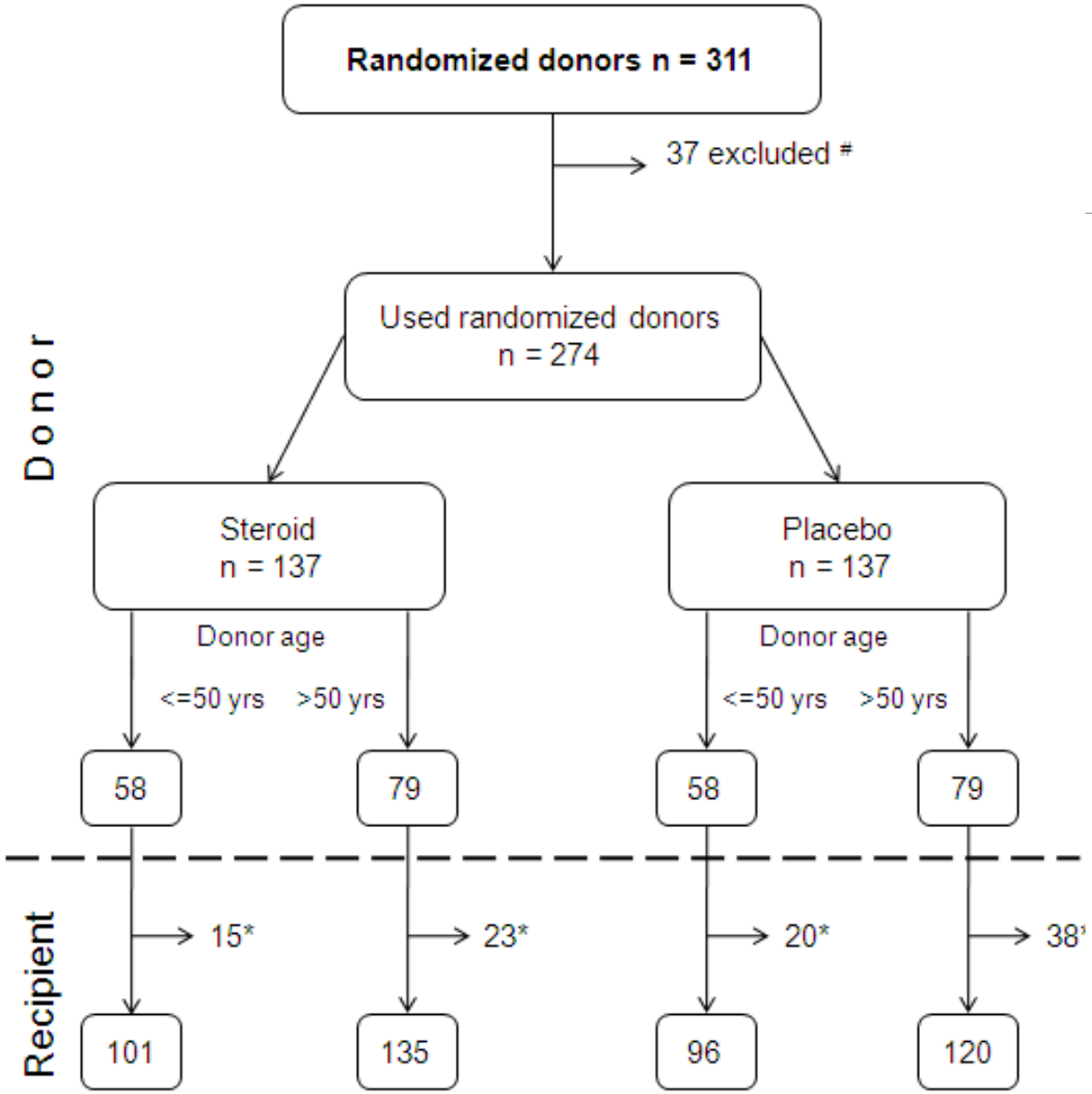
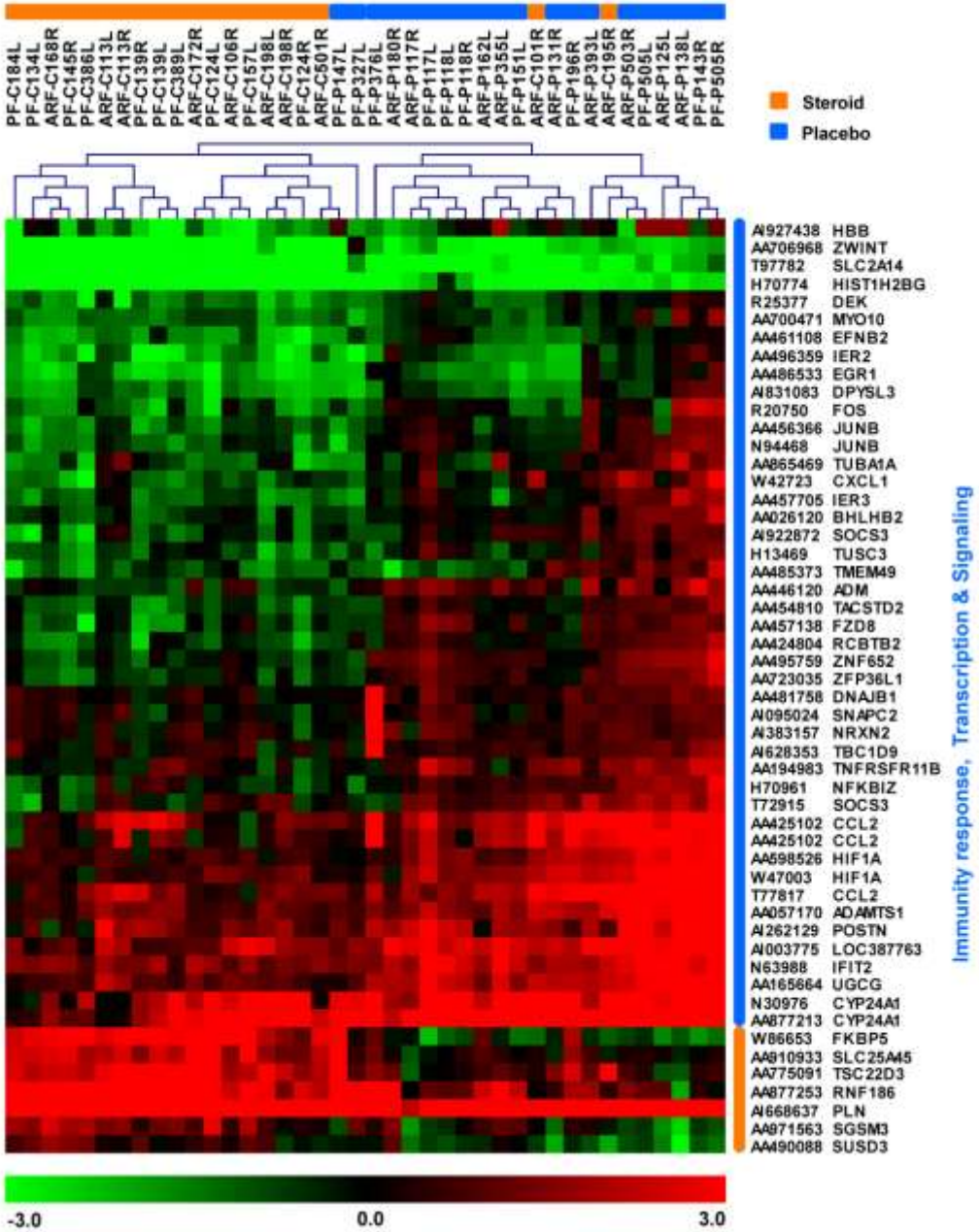


Ann Intern Med. 2010;153:222-230

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

Steroid treatment suppressed inflammation



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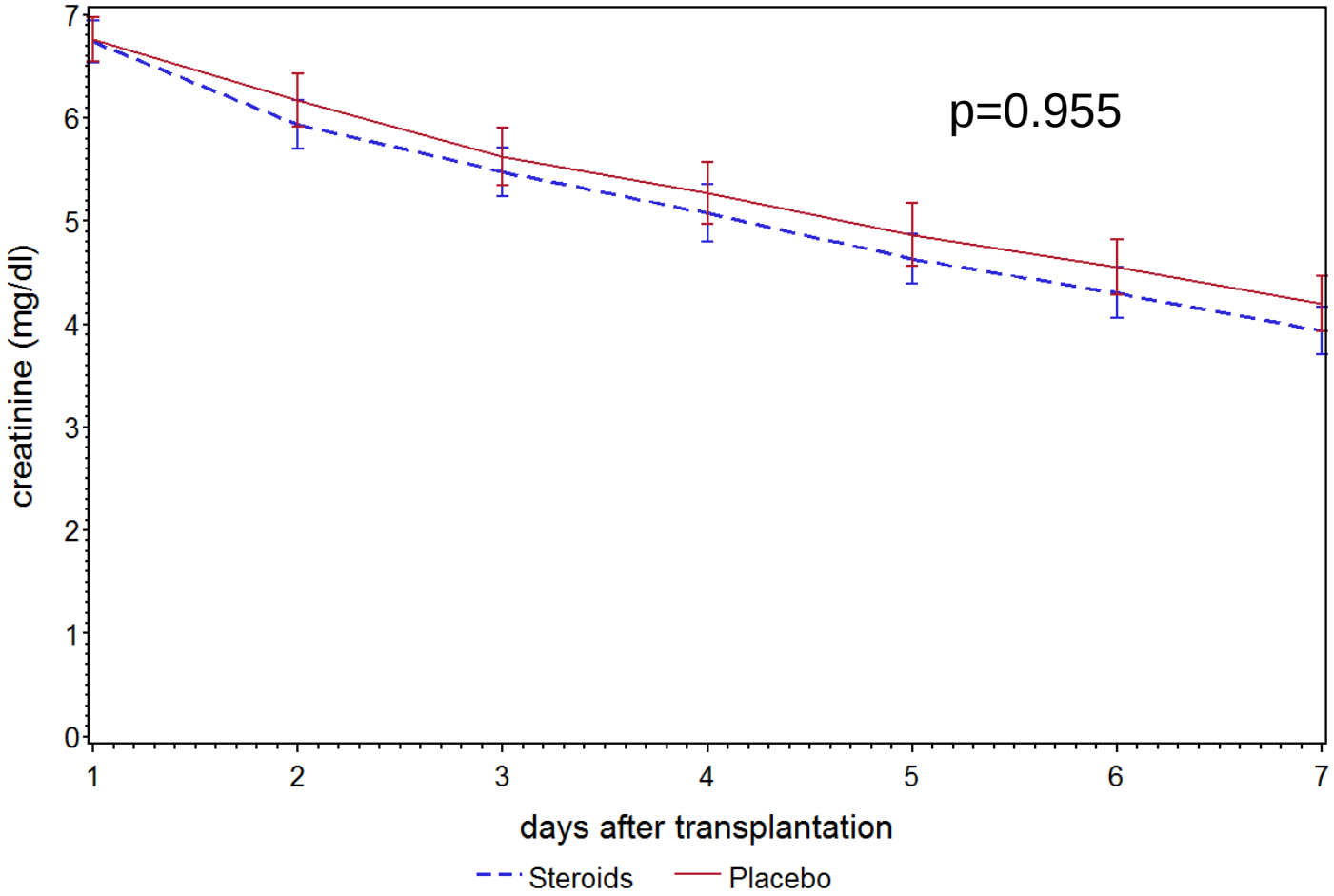
Primary study end point - DGF

	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

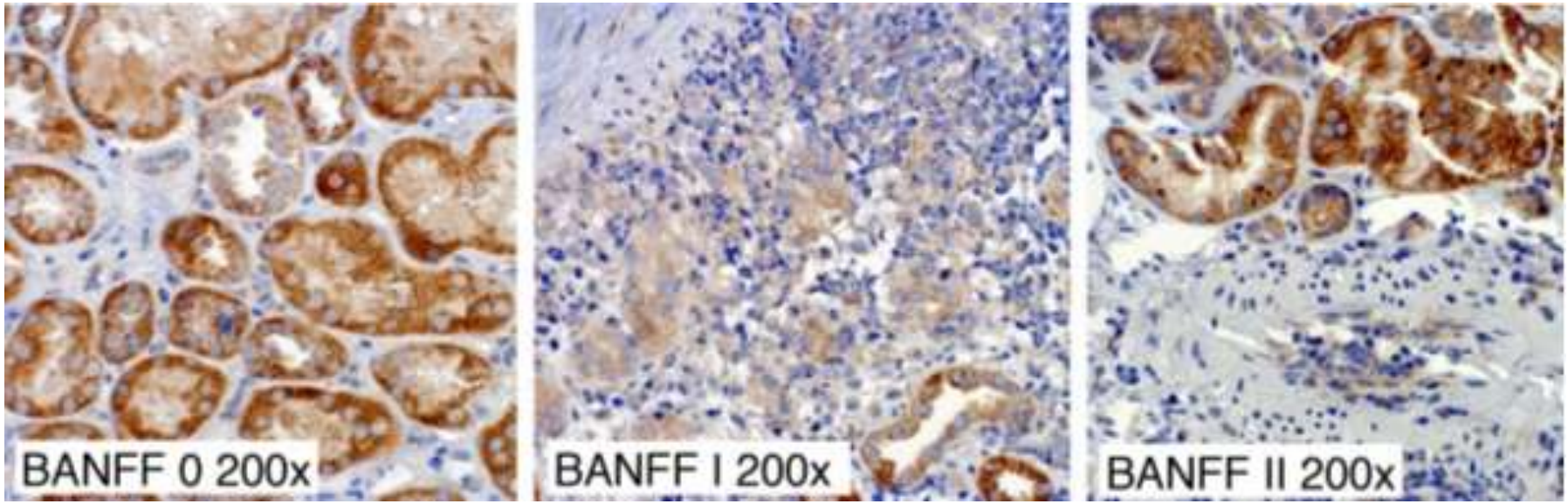
Ann Intern Med. 2010;153:222-230

Creatinine Trajectories



Ann Intern Med. 2010;153:222-230

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

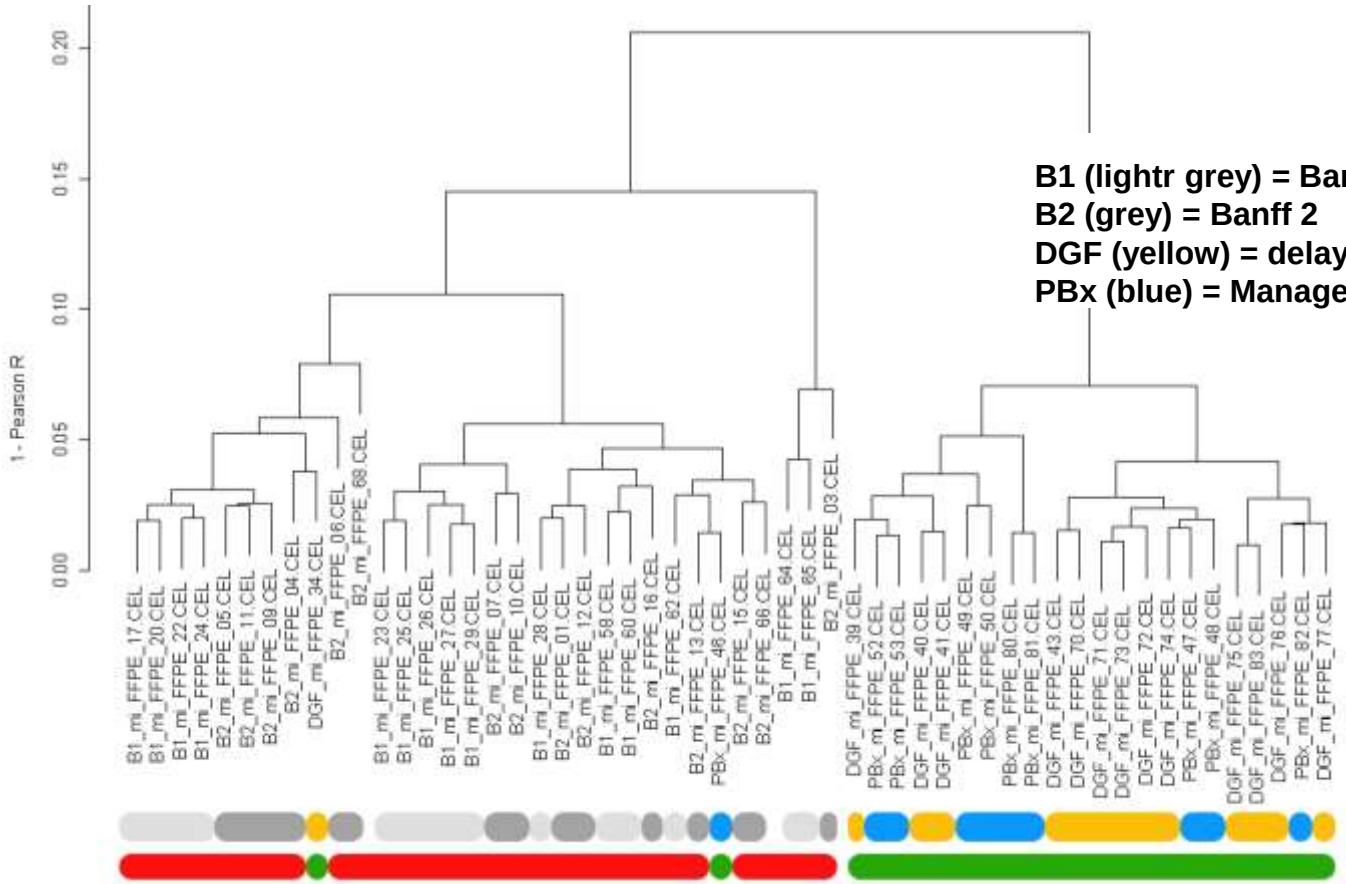


DICER

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)



B1 (lightr grey) = Banff 1
B2 (grey) = Banff 2
DGF (yellow) = delayed graft function
PBx (blue) = Management biopsies

Wilflingseder J et al. 2010

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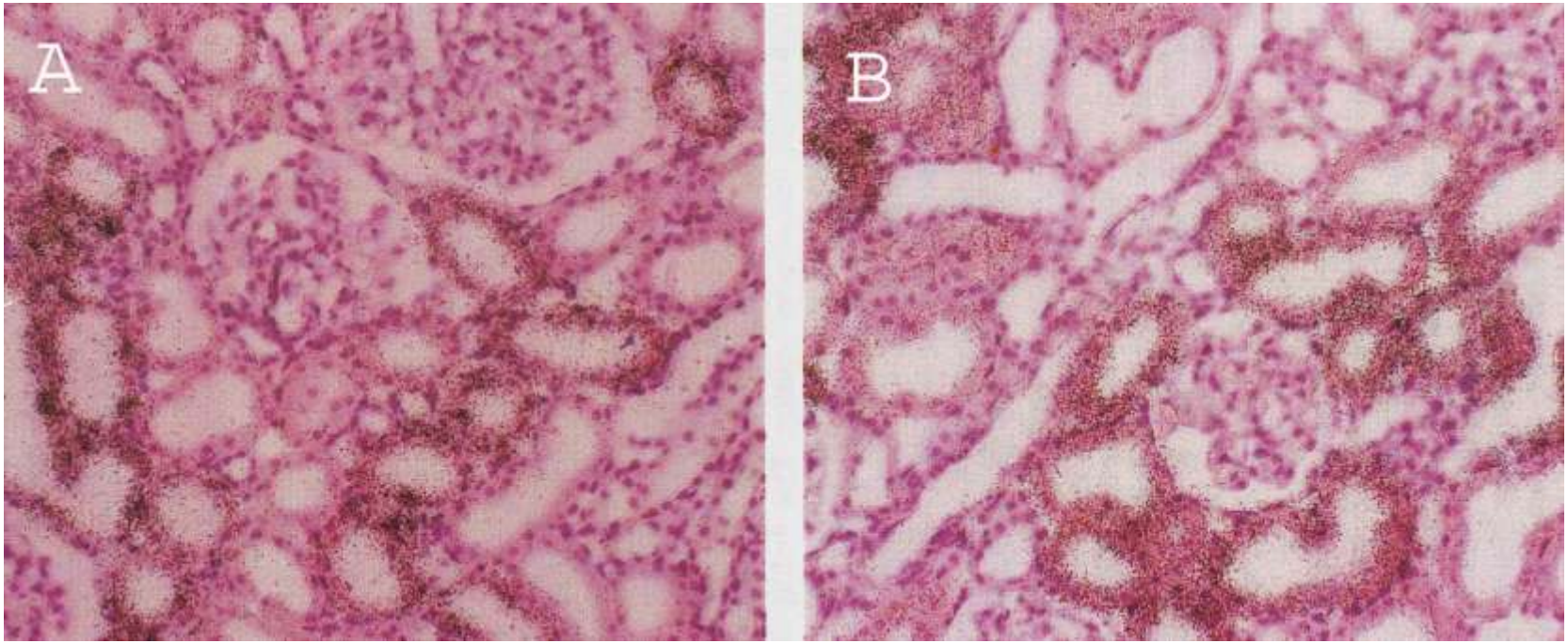
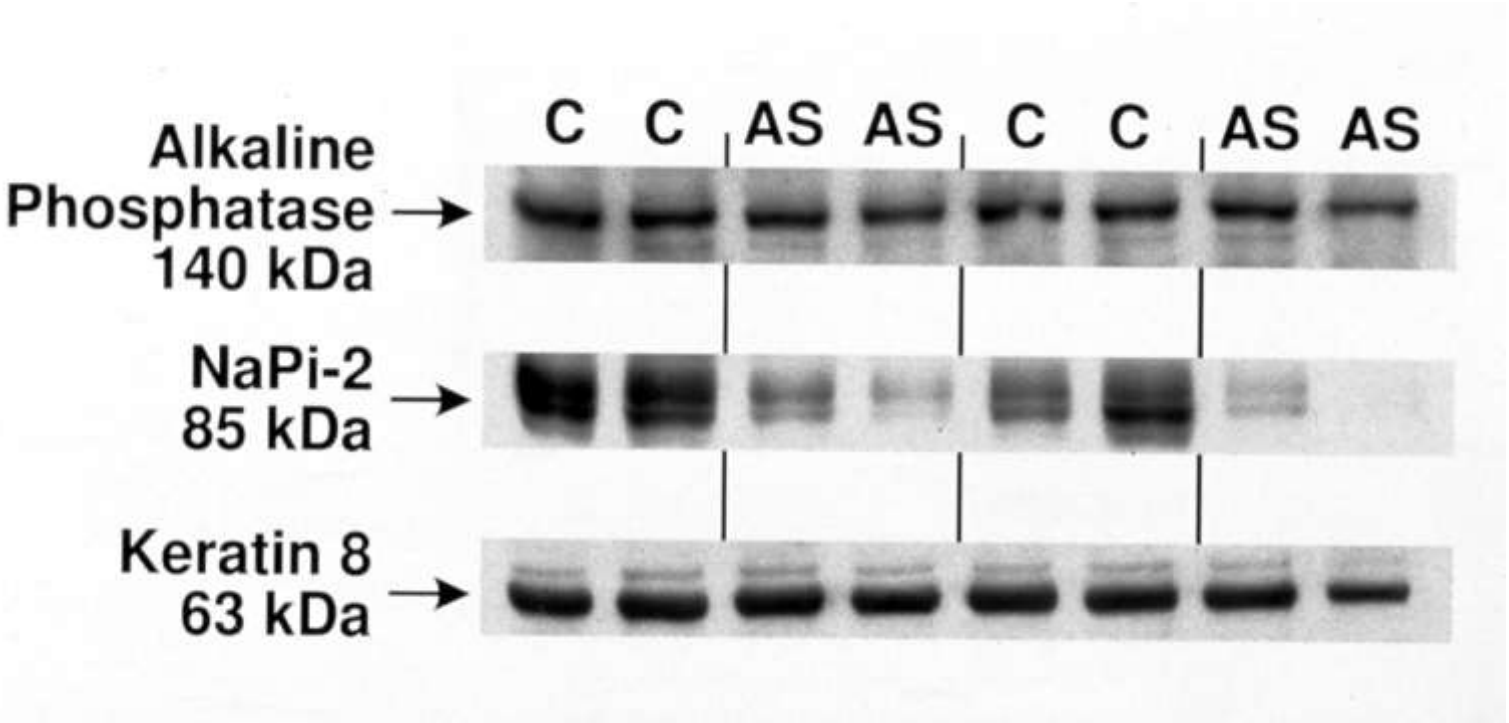
Antisense DNA/siRNA



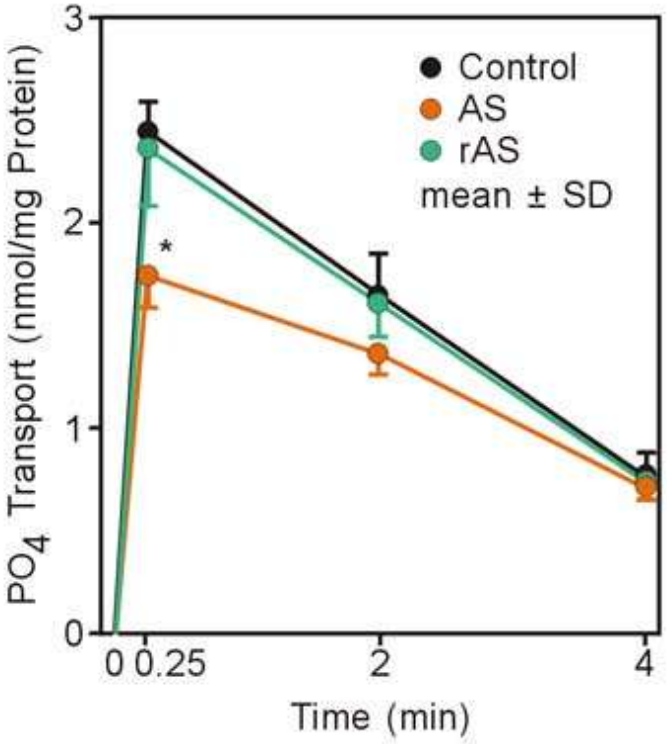
Oberbauer R et al. Kidney Int 1995, 48:1226-1232

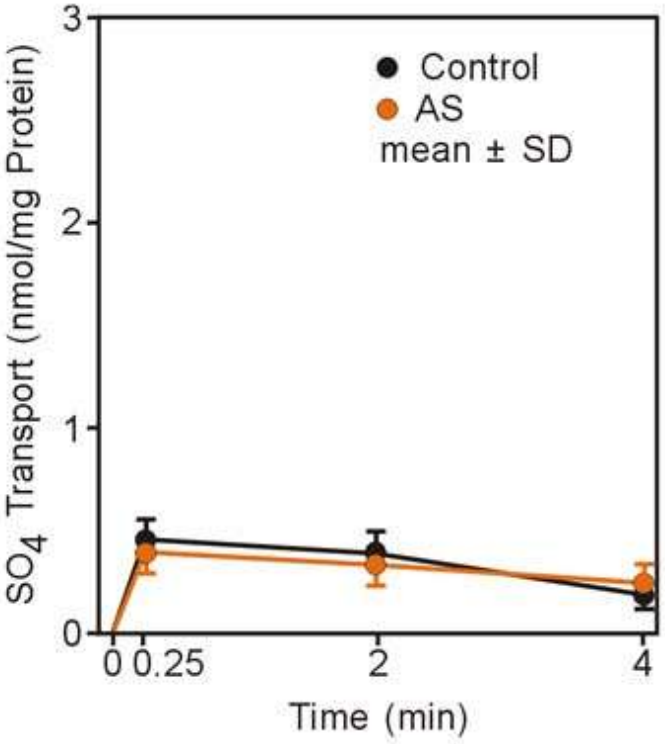
Antisense DNA/siRNA



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

Antisense DNA/siRNA





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

Acknowledgments

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