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Elisabethinen Linz

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

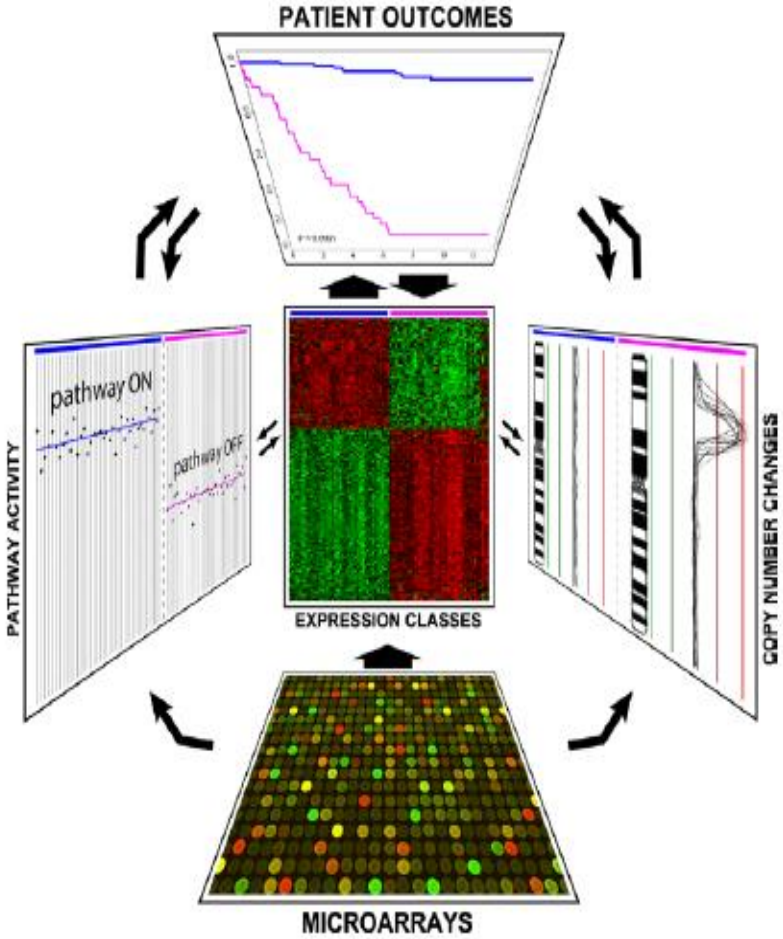
Rainer Oberbauer (30+10min)

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

Genomics

23andMe + Google

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https://www.23andme.com

What your DNA says about you.

Find out things like if your body metabolizes caffeine quickly, or if you're at a higher risk for diabetes. The more you know about your DNA, the more you know about yourself.

Carrier status

Find out if your children are at risk for inherited conditions, so you can plan for the health of your family.

Health risks

Understand your genetic health risks. Change what you can, manage what you can't.

Drug response

Arm your doctor with information on how you might respond to certain medications.

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about us

Mission Statement

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

A Snapshot of Team 23andMe

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next

67% of us have a family history of cancer

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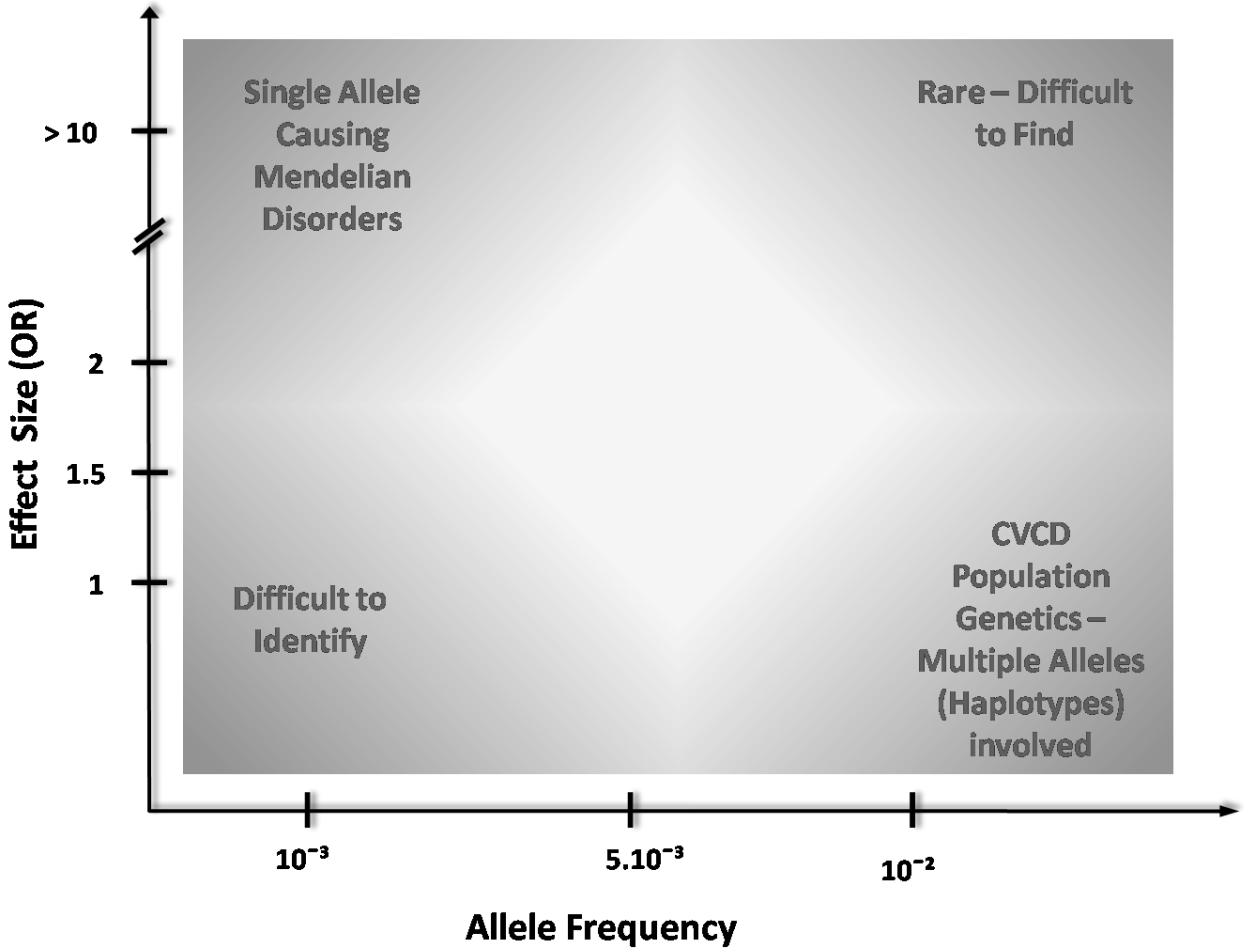
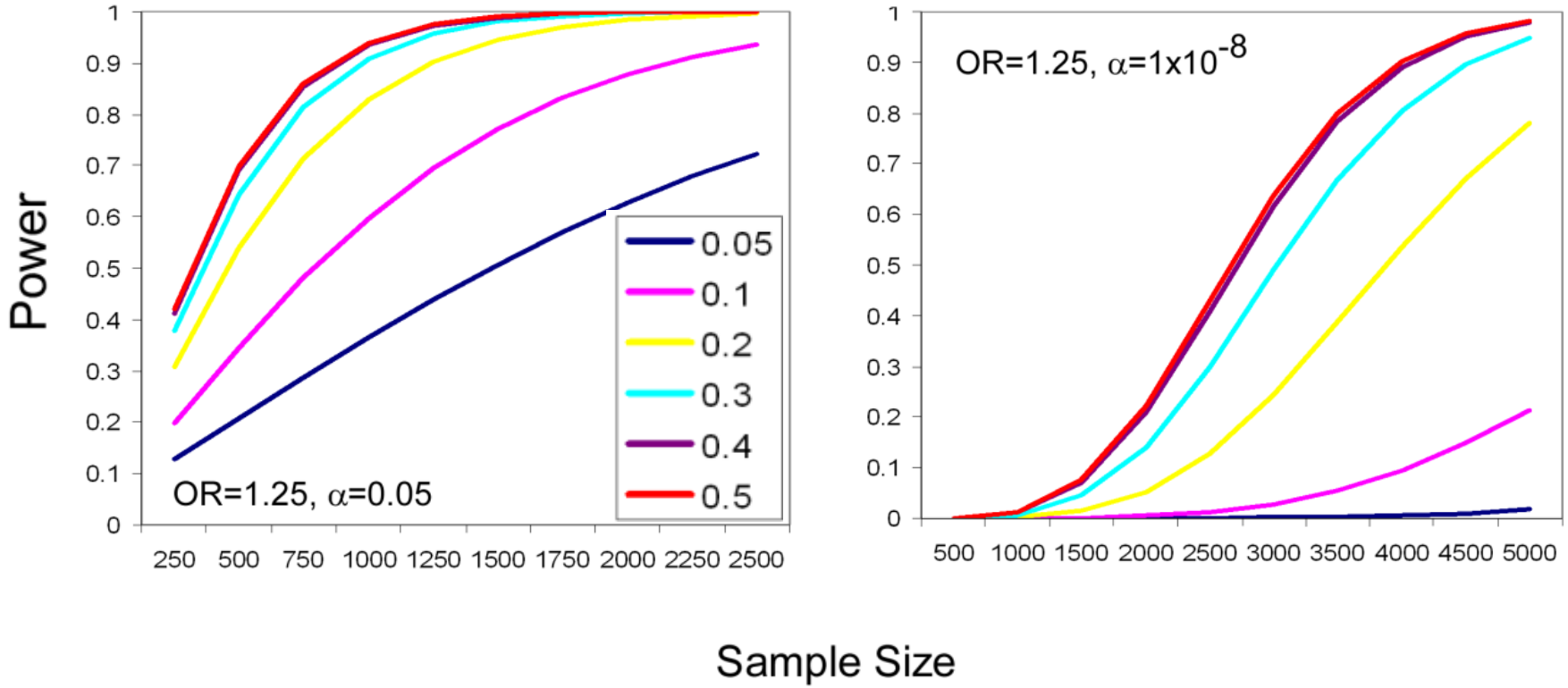
Allele frequencies and effect sizes of genetic variants in human diseases - GWAS



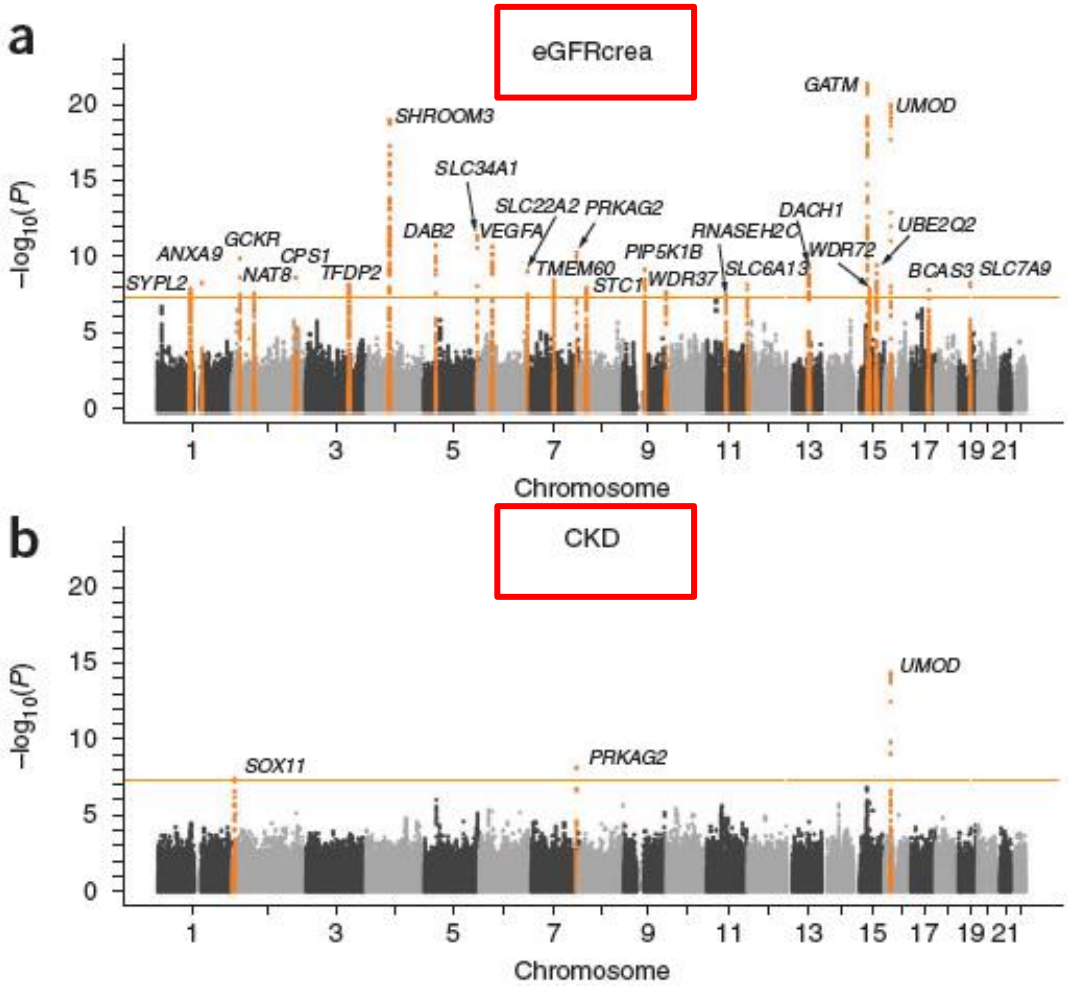
Le, Y, Shiffman D, Oberbauer R. MMB 2010 (in press)

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

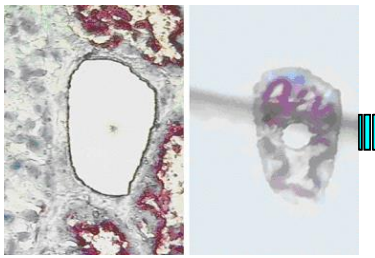
Systems biology of kidney injury

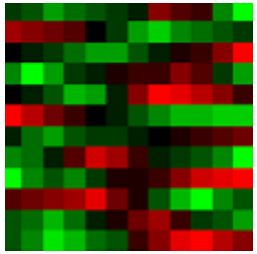
Laser Capture
Microdissection
Of Donor Kidneys

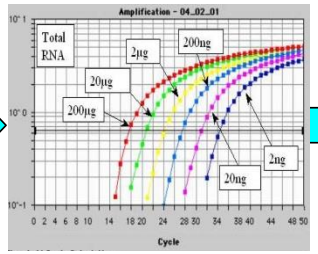
DNA
Microarrays

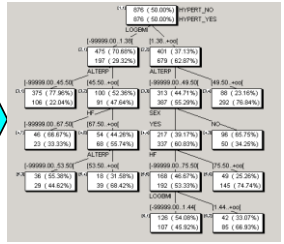
Quantitative
PCR

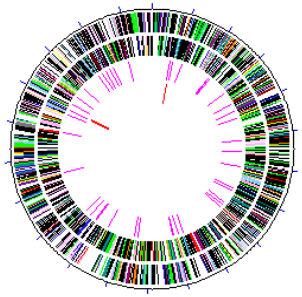
Data
Mining

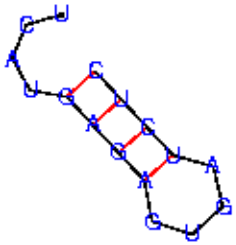


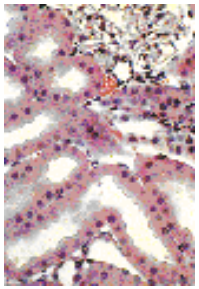


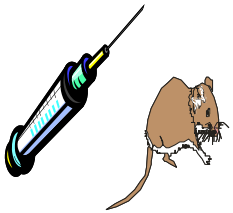












Target Gen
Definition

Antisense
Nucleotide
Design &
Synthese

In vitro
POC

In vivo
POC

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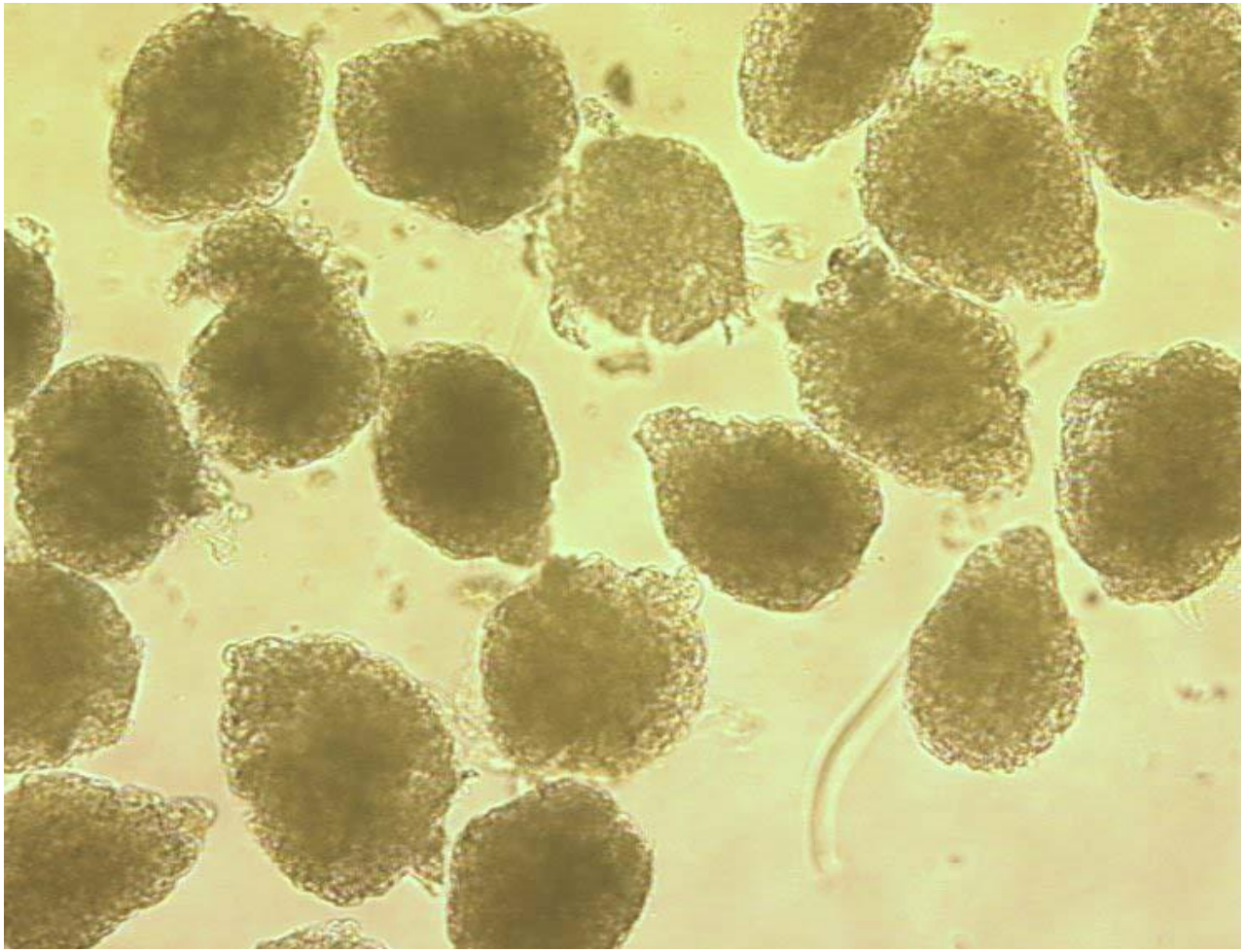
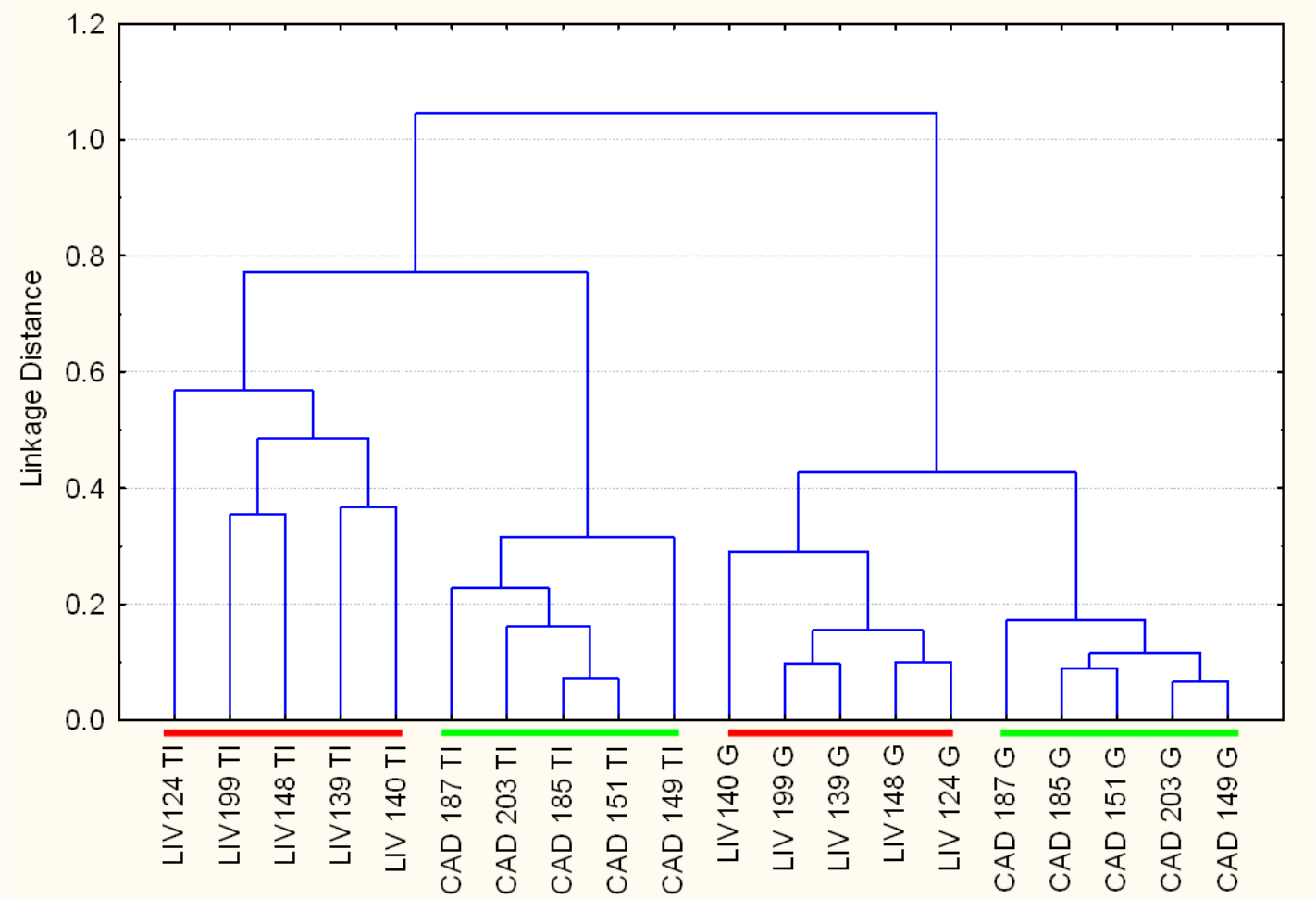
Glomeruli isolated from live and deceased donor kidney biopsies



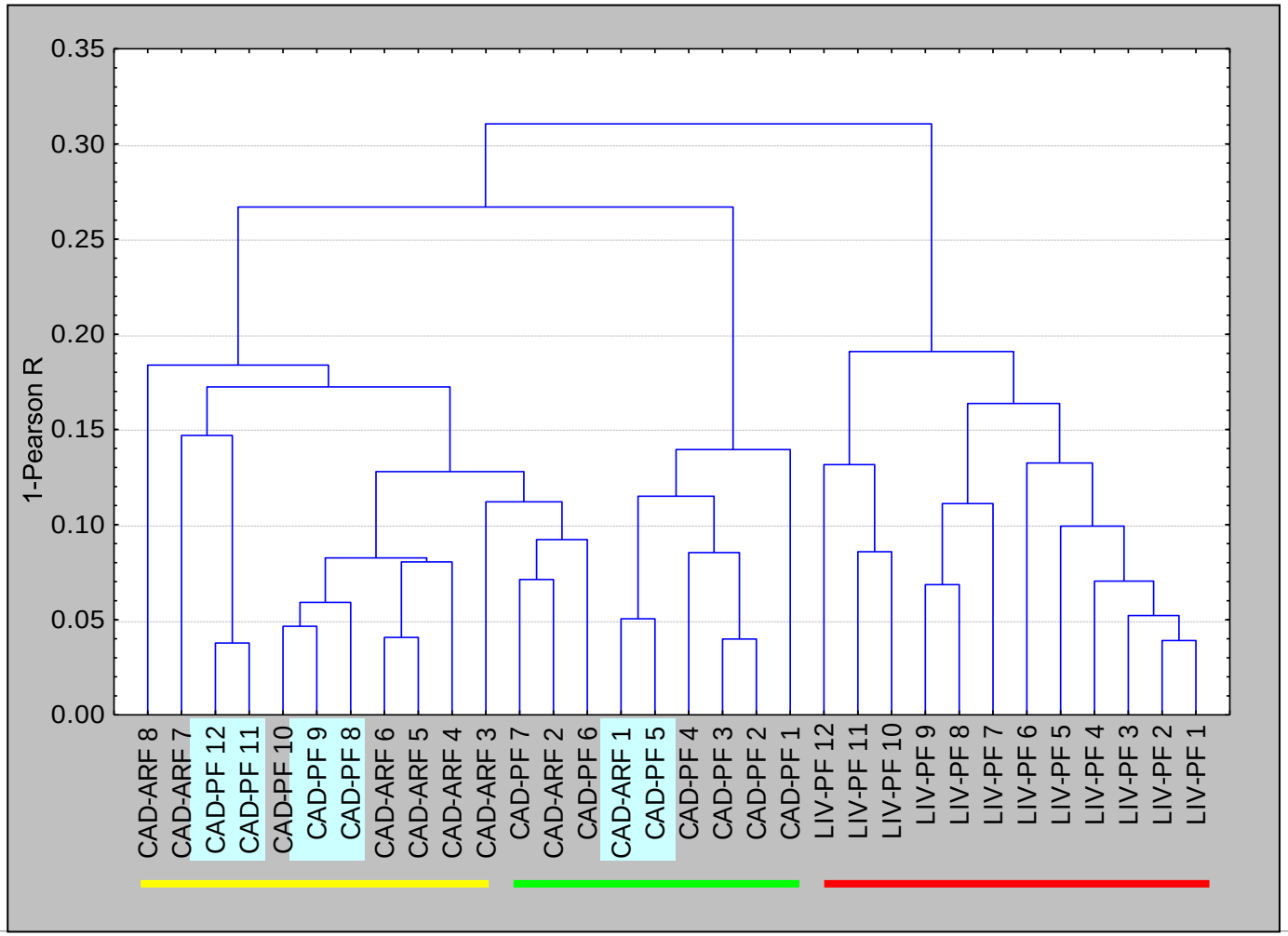
Kainz A et al. *Am J Transplant* 2004; 4:1595-1604

Transcripts are specific for deceased and live donor kidney compartments



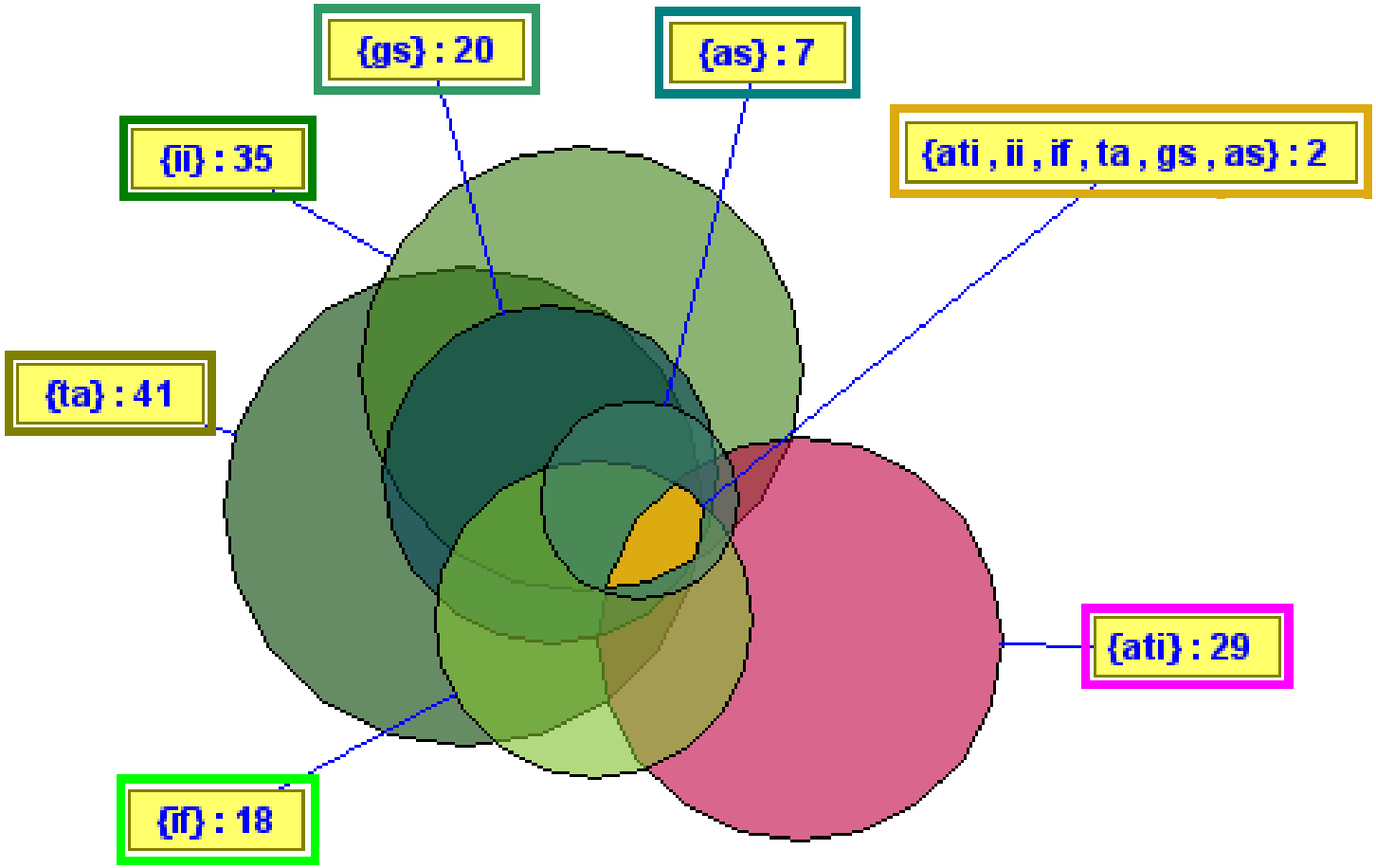
Kainz A et al. Am J Transplant 2004; 4:1595-1604

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.*

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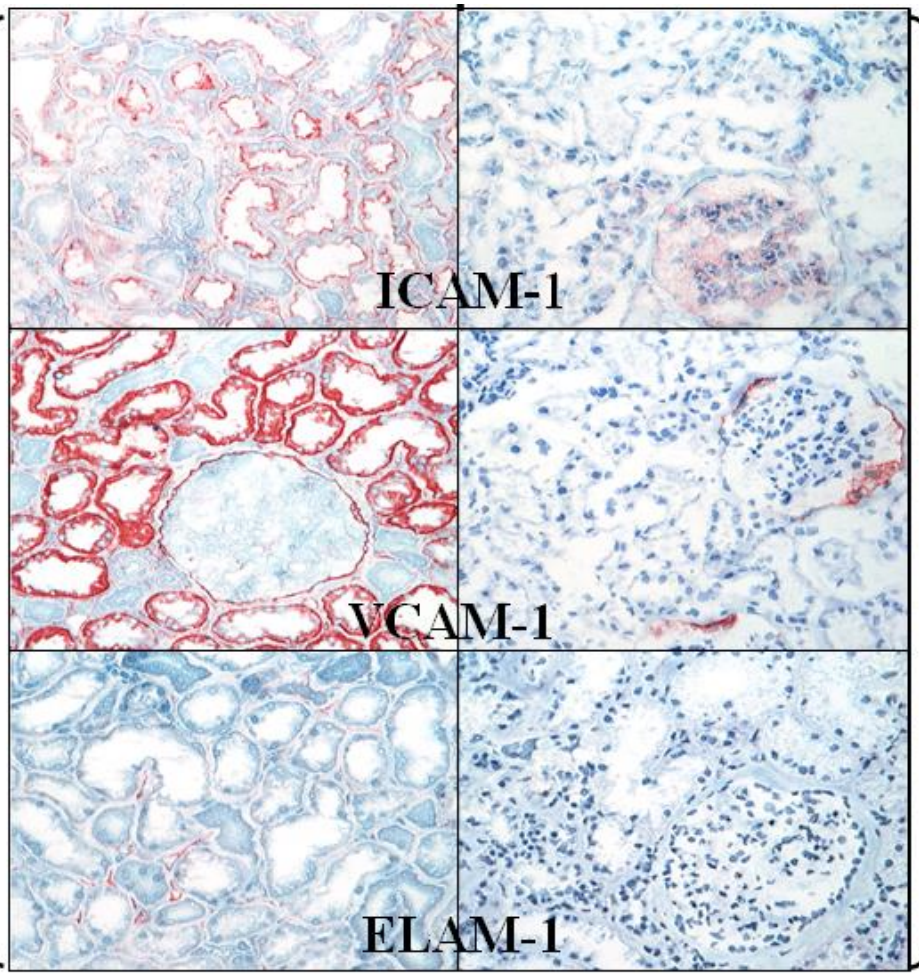
Inflammation in Deceased Donor Kidney Biopsies

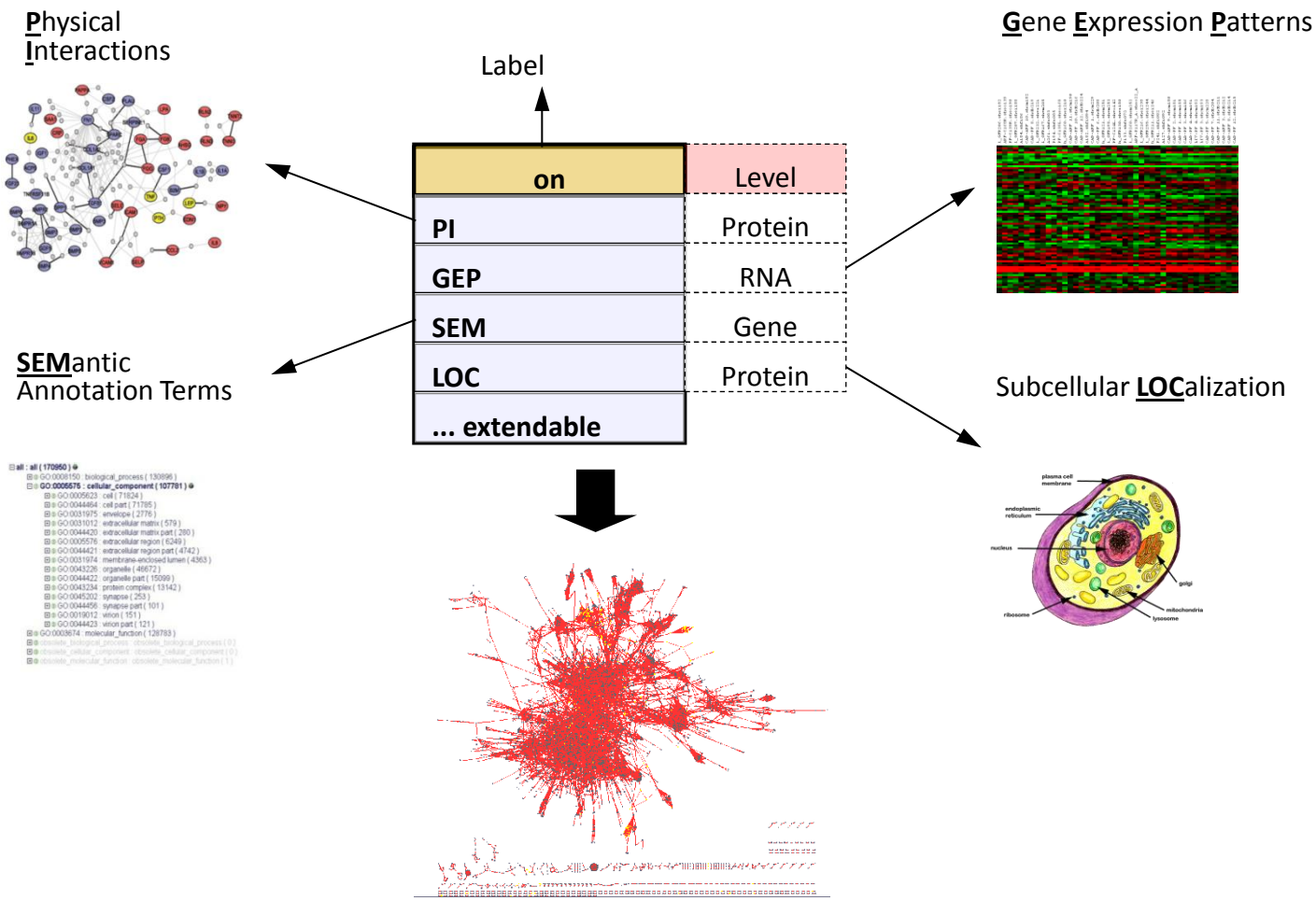
DGF



PGF

Schwarz et al Transplantation 2001:71:1666-72

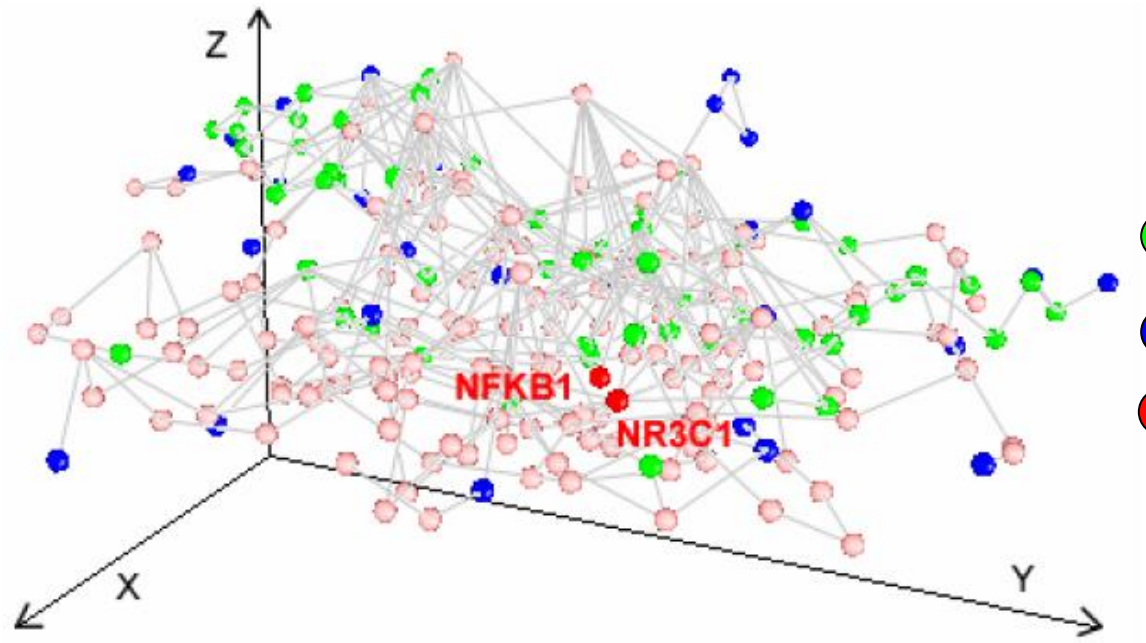
Systems Biology and omicsNET



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

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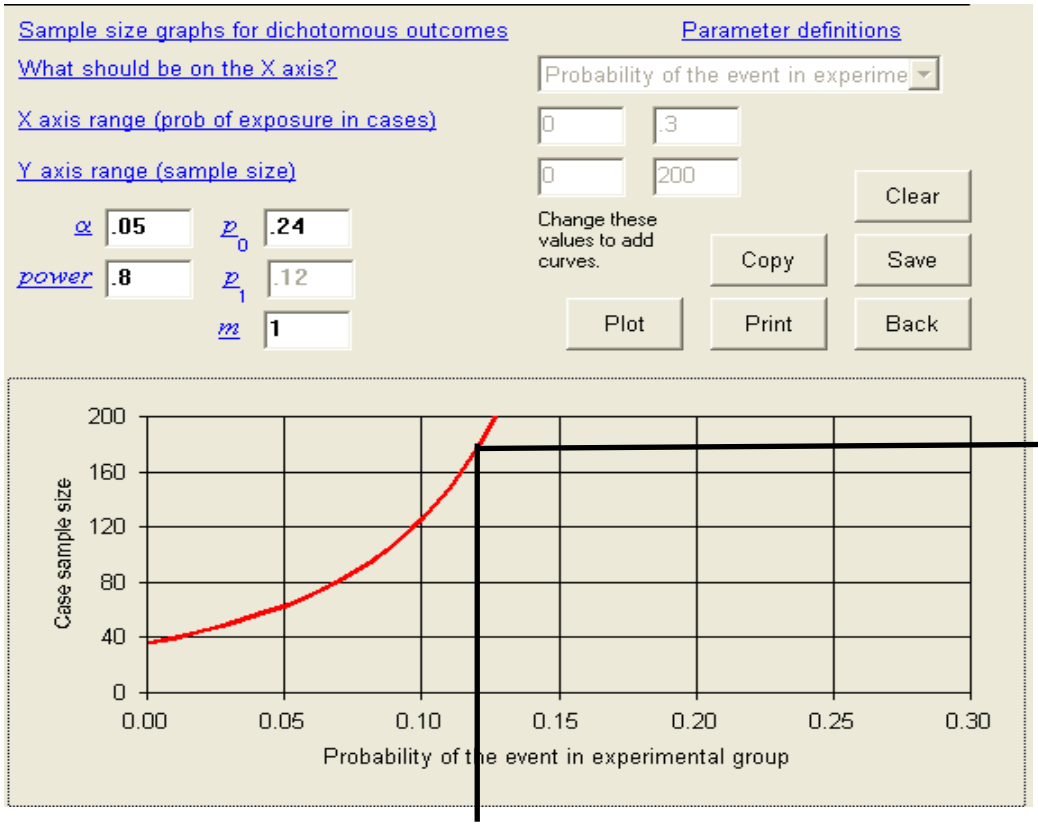
A Multicenter Double-Blinded RCT of Deceased Organ Donor Pre-Treatment with Corticosteroids for the Prevention of Postischemic Acute Renal Allograft Failure

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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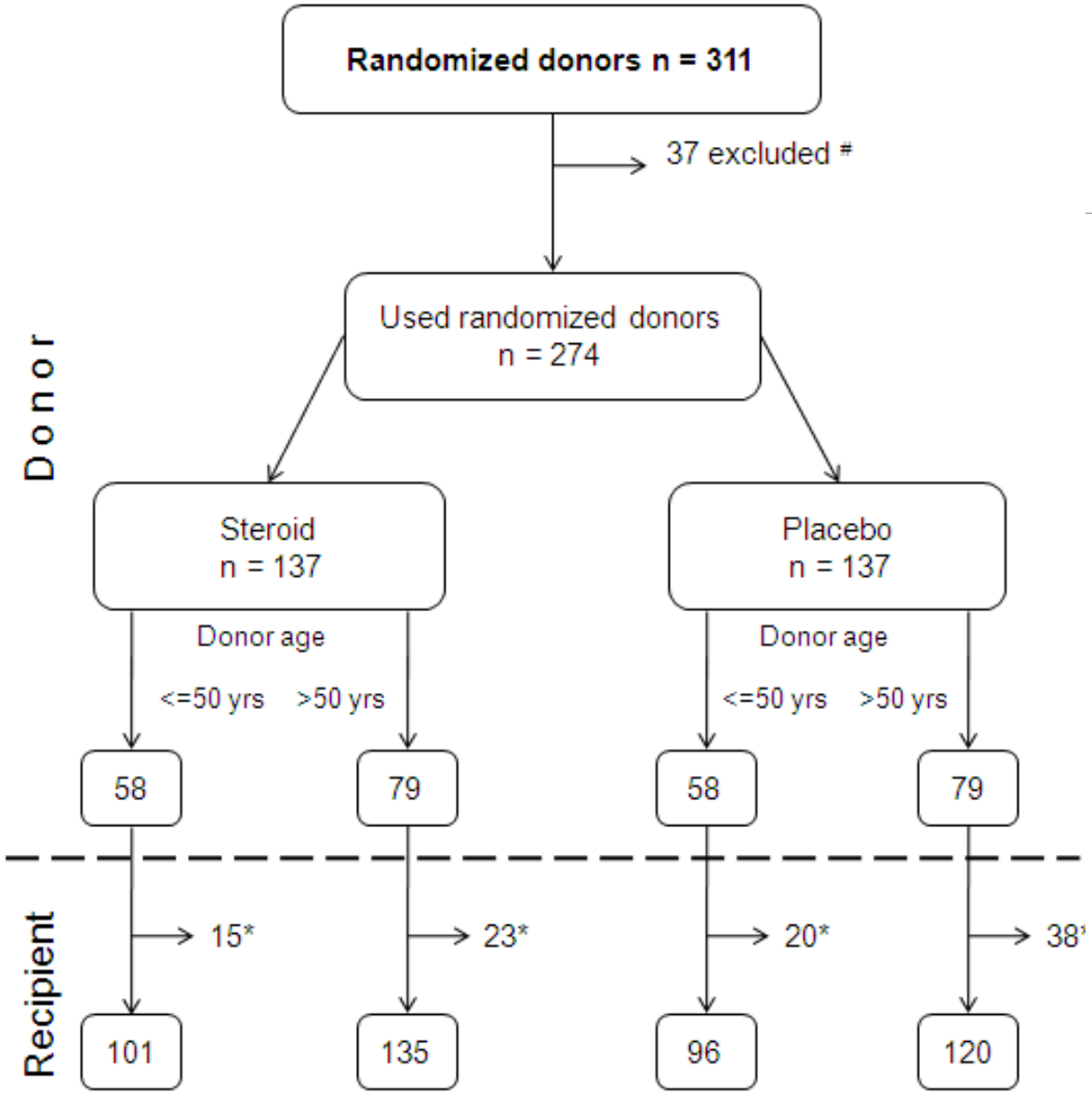
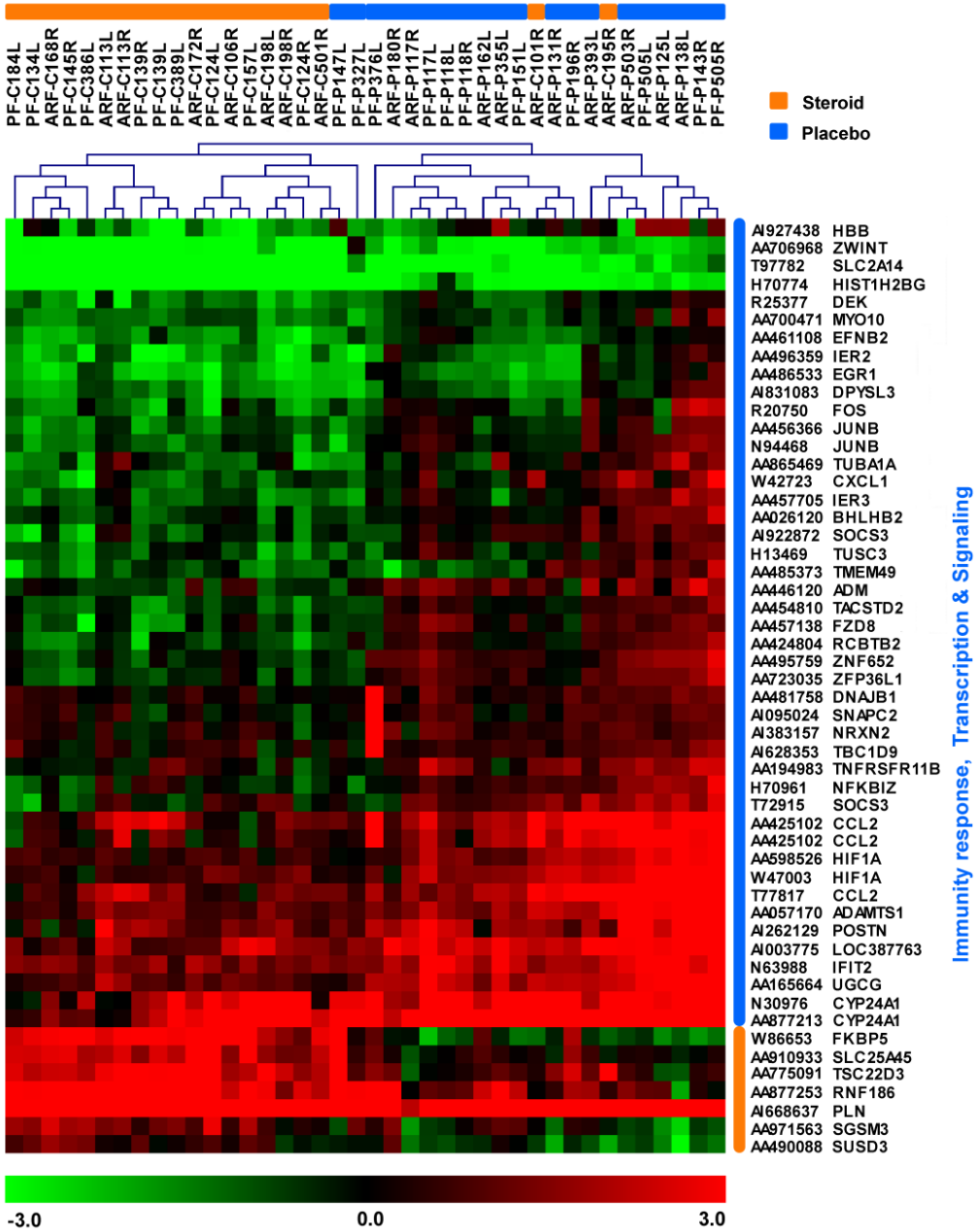


Ann Intern Med. 2010;153:222-230

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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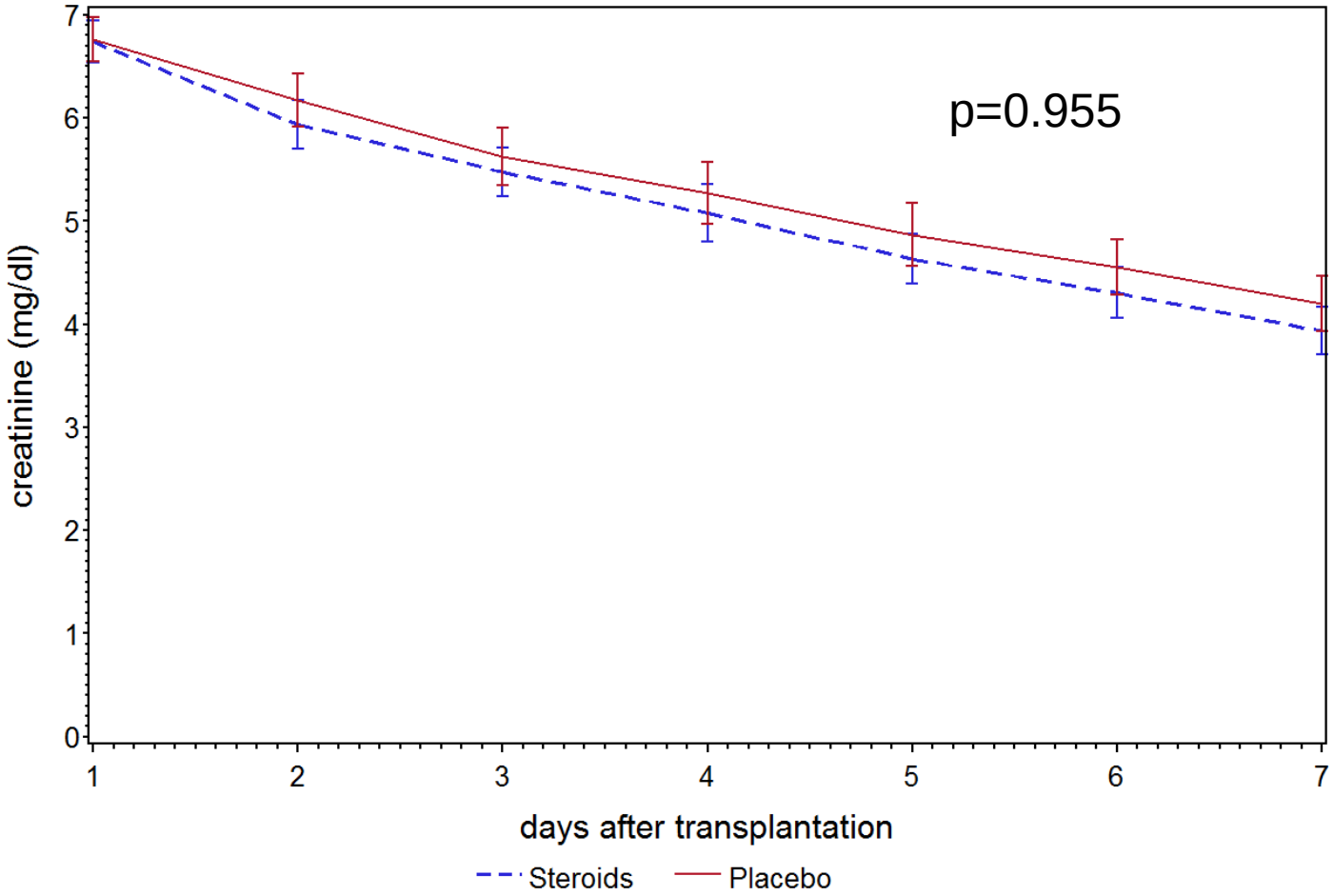
Primary study end point - DGF

	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

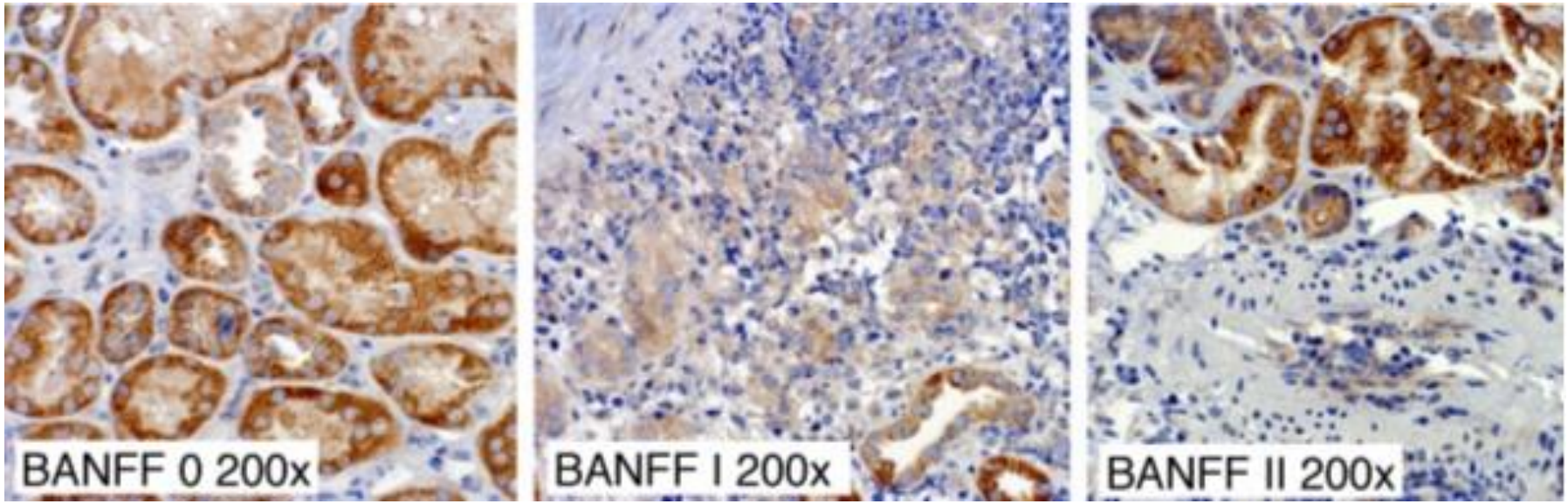
Ann Intern Med. 2010;153:222-230

Creatinine Trajectories



Ann Intern Med. 2010;153:222-230

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

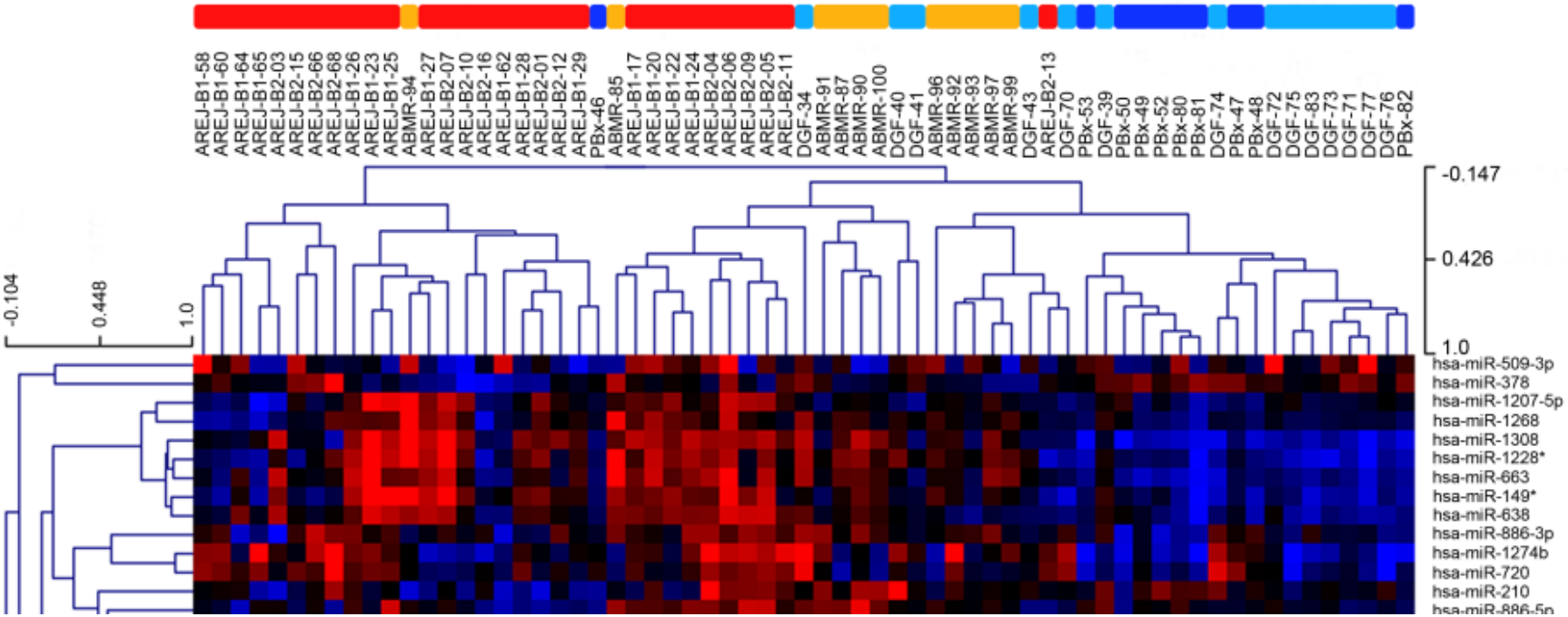


DICER

code for a complex cellular phenotype by silencing of target mRNAs

Soleiman A 2009

miRNA Profiles discriminate post-transplant events



Wilflingseder J et al. Transplantation 2013; 95(6):835-41.

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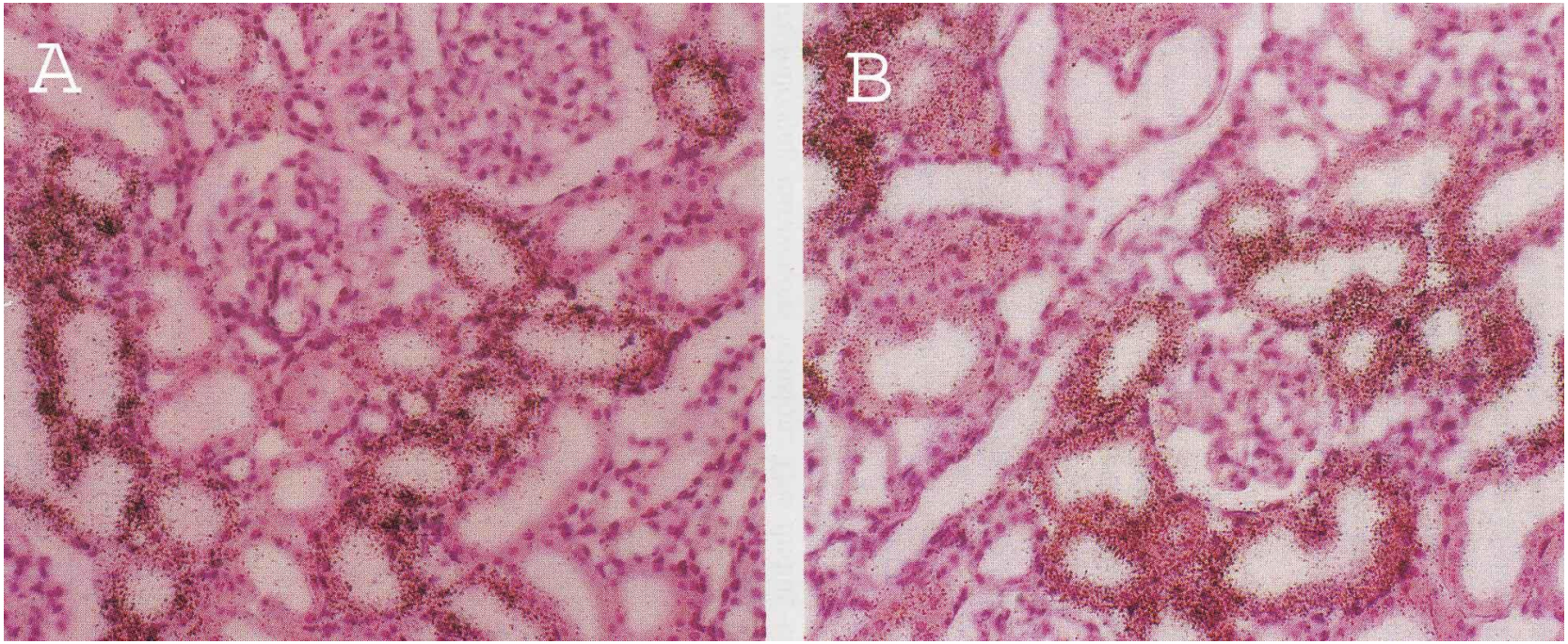
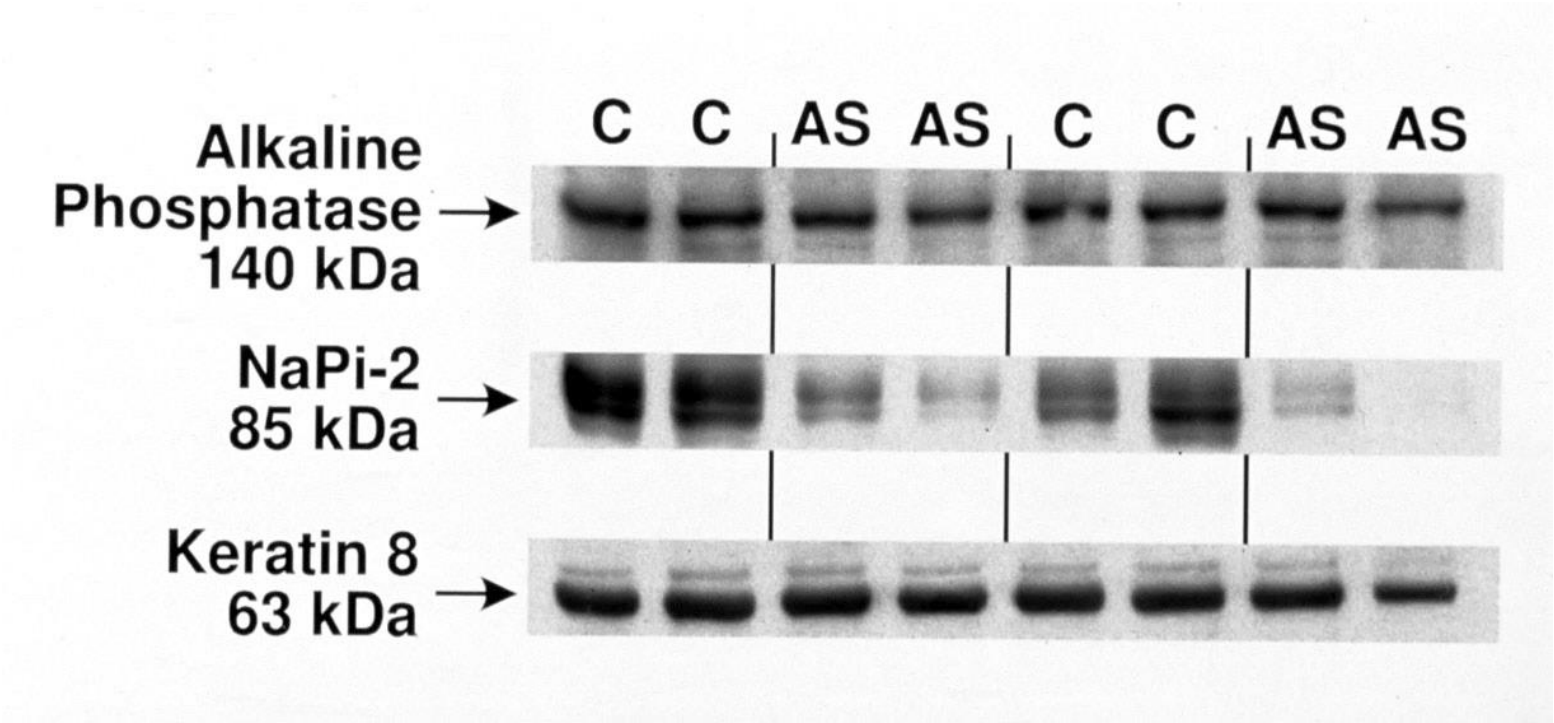
Antisense DNA/siRNA



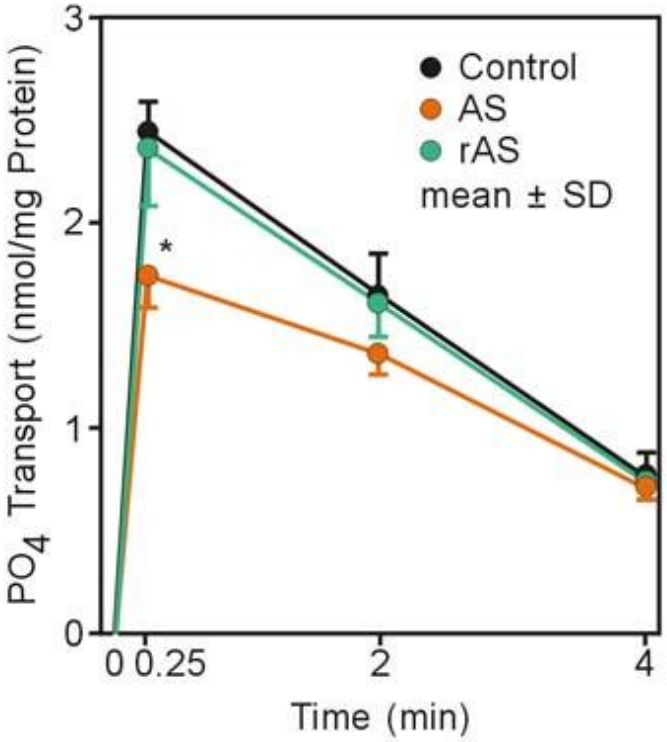
Oberbauer R et al. Kidney Int 1995, 48:1226-1232

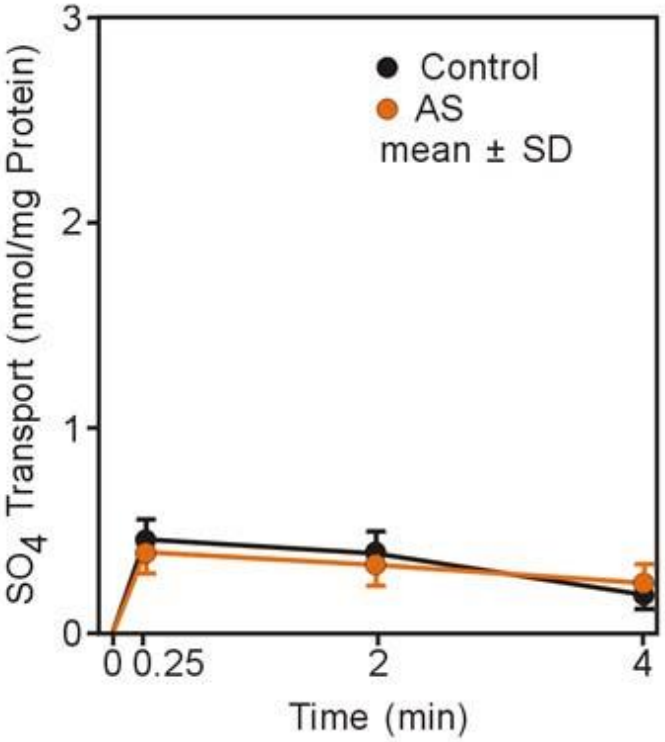
Antisense DNA/siRNA



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

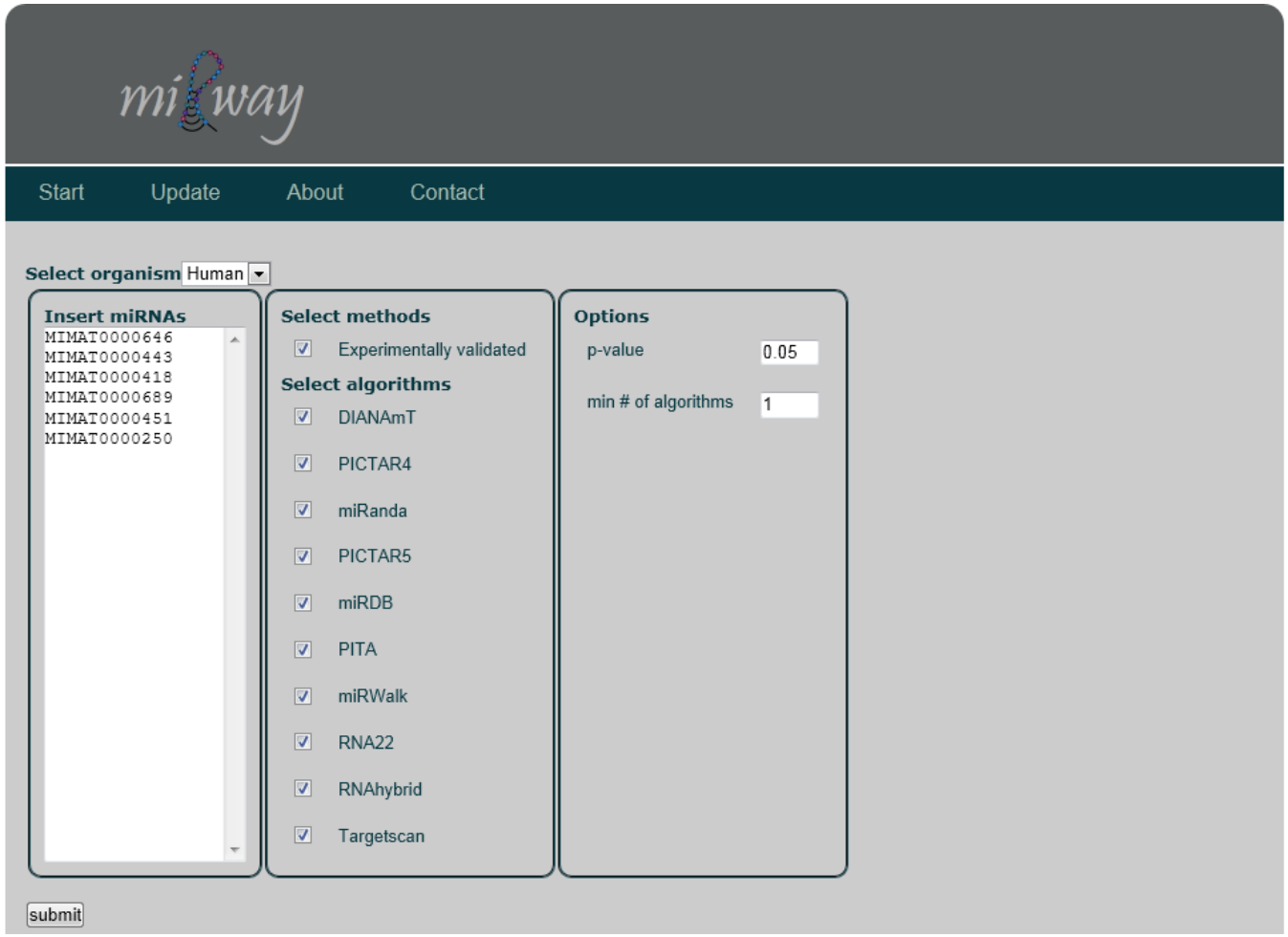
Antisense DNA/siRNA





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

miRNA prediction tool



Ivcevic S, Stütz C et al. 2013

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KH Elisabethinen

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