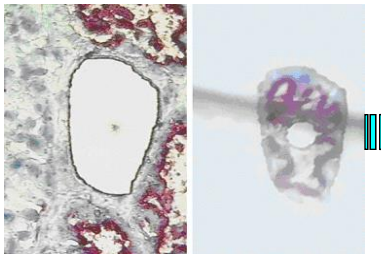
Omics technologies in donor kidneys to reduced DGF

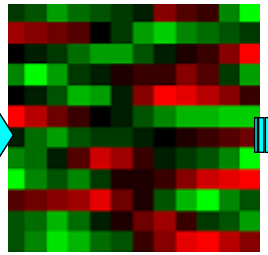
Rainer Oberbauer

Workplan 2003-2017: Systems biology of allograft injury

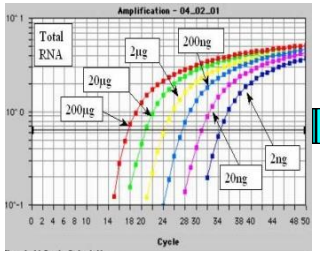
LCM



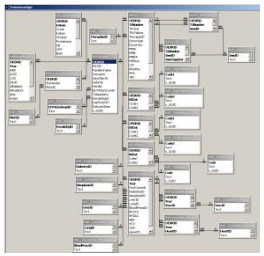
Omics



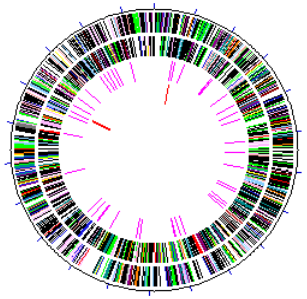
QC



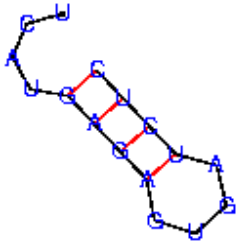
OEDTR



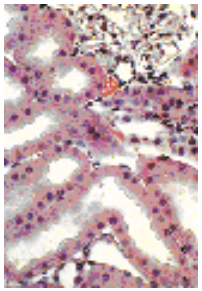
Integrative Analysis



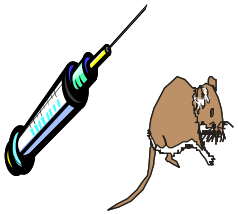
Target Gene Definition



Antisense Design & Synthesis



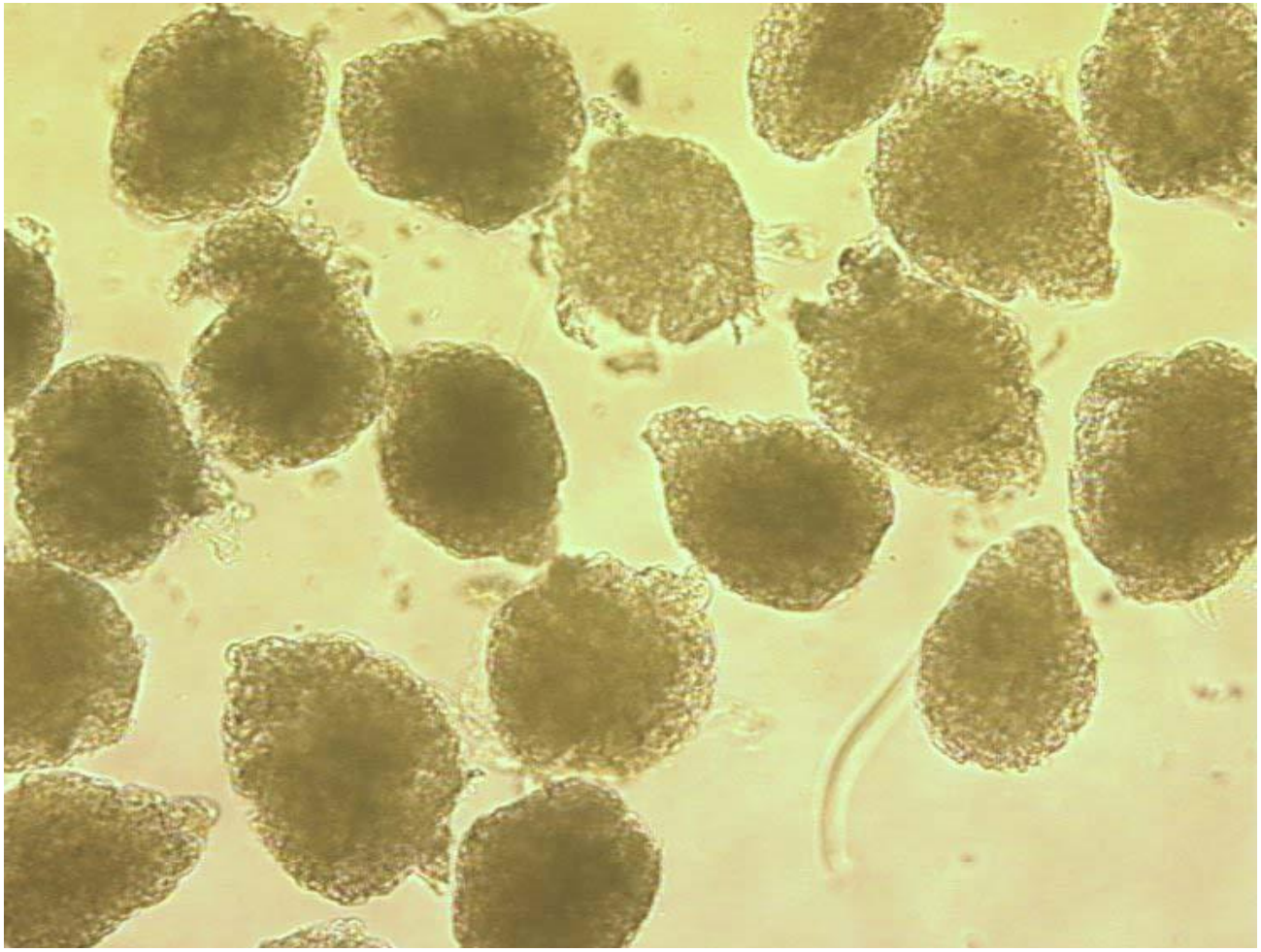
In vitro POC



In vivo POC

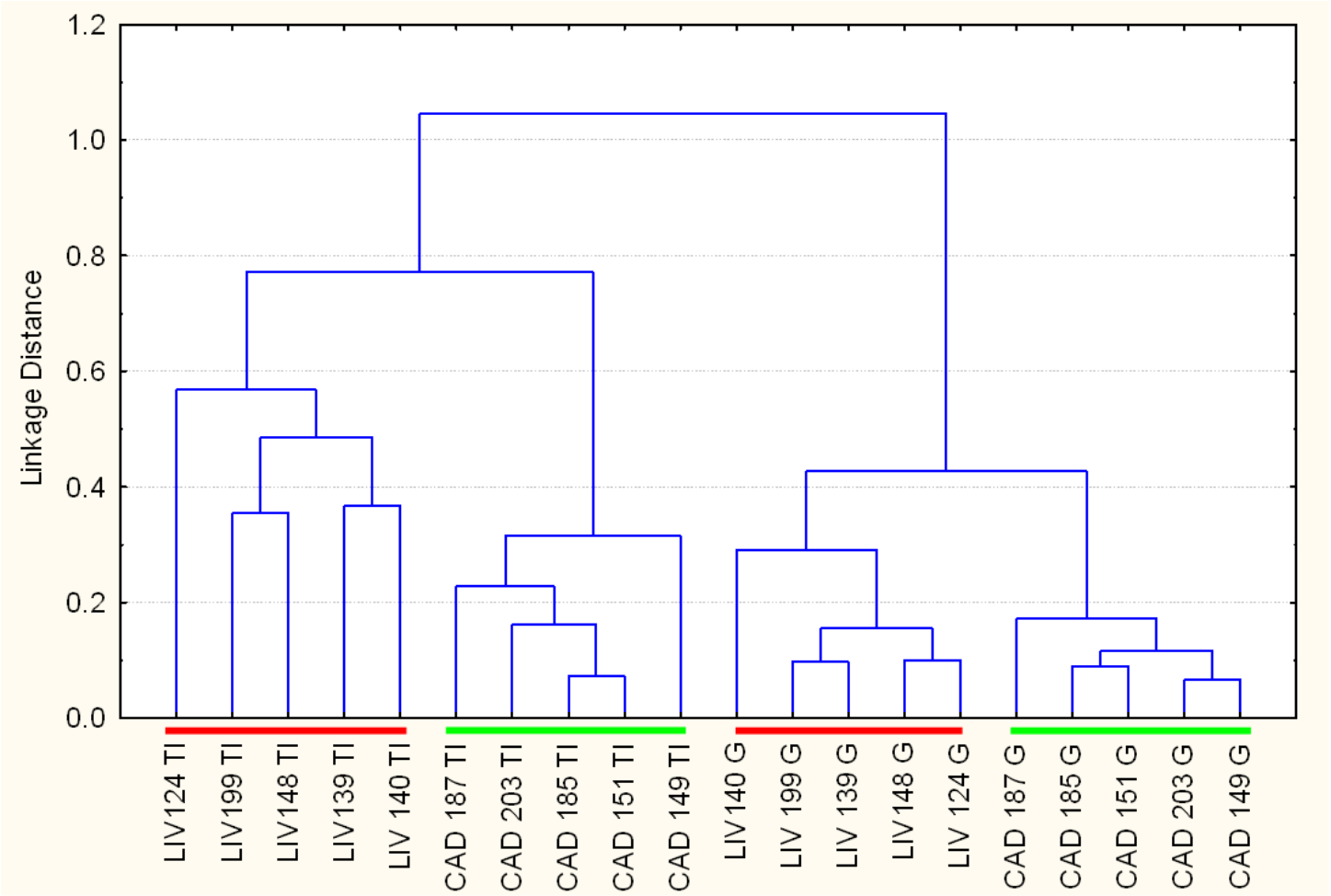
Clinical POC

Glomeruli isolated from live and deceased donor kidney biopsies



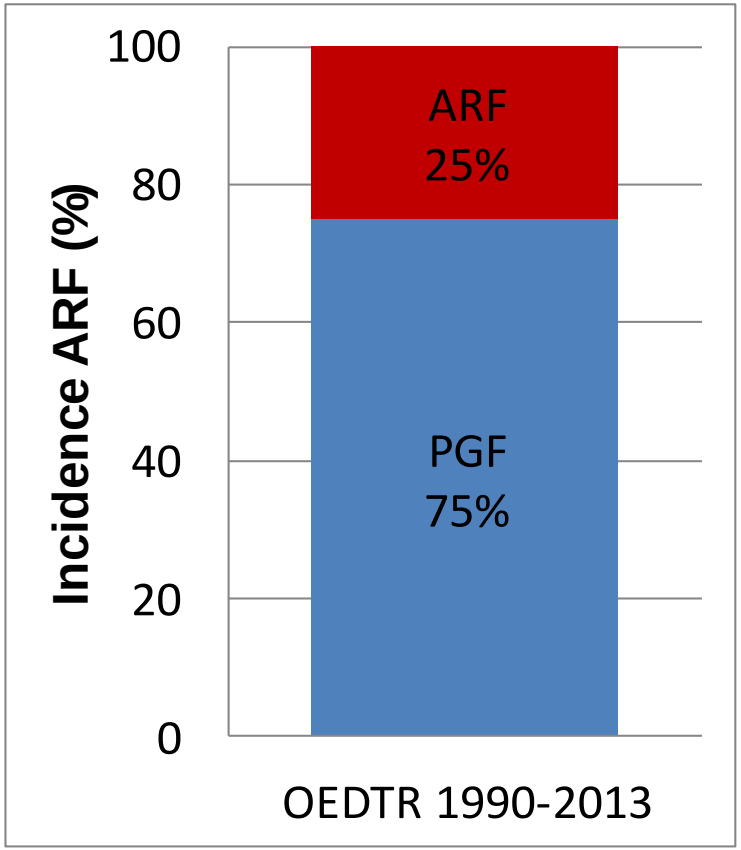
Kainz A et al. *Am J Transplant* 2004; 4:1595-1604

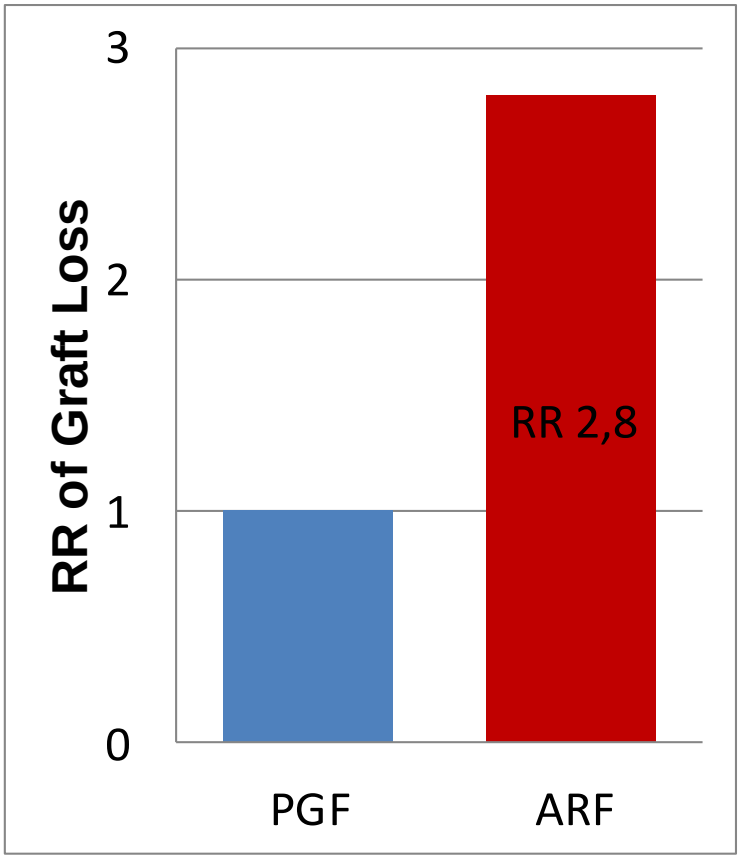
Transcripts are specific for deceased and live donor kidney compartments



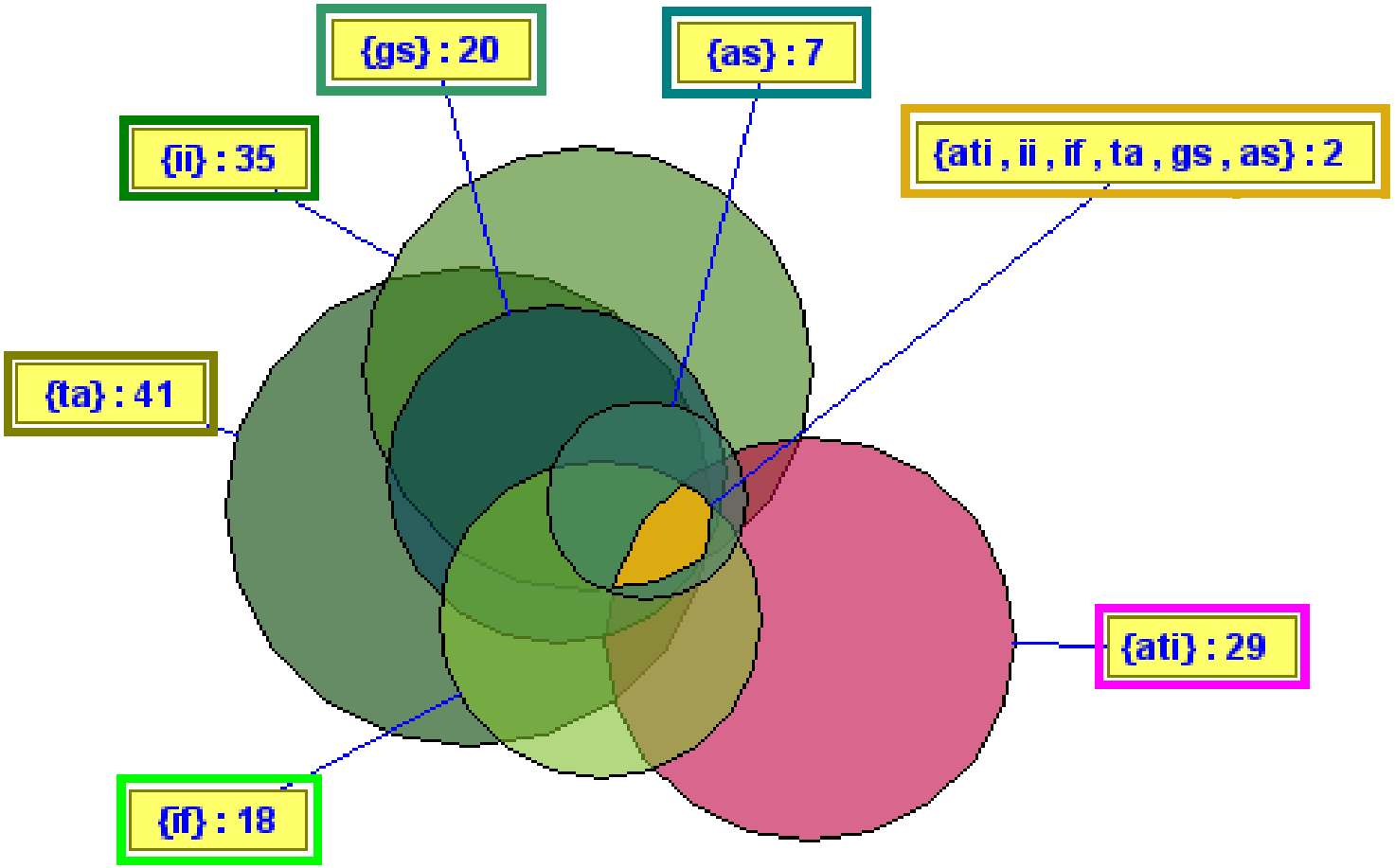
Kainz A et al. Am J Transplant 2004; 4:1595-1604

Post-Transplant ARF/DGF: Incidence & Consequences





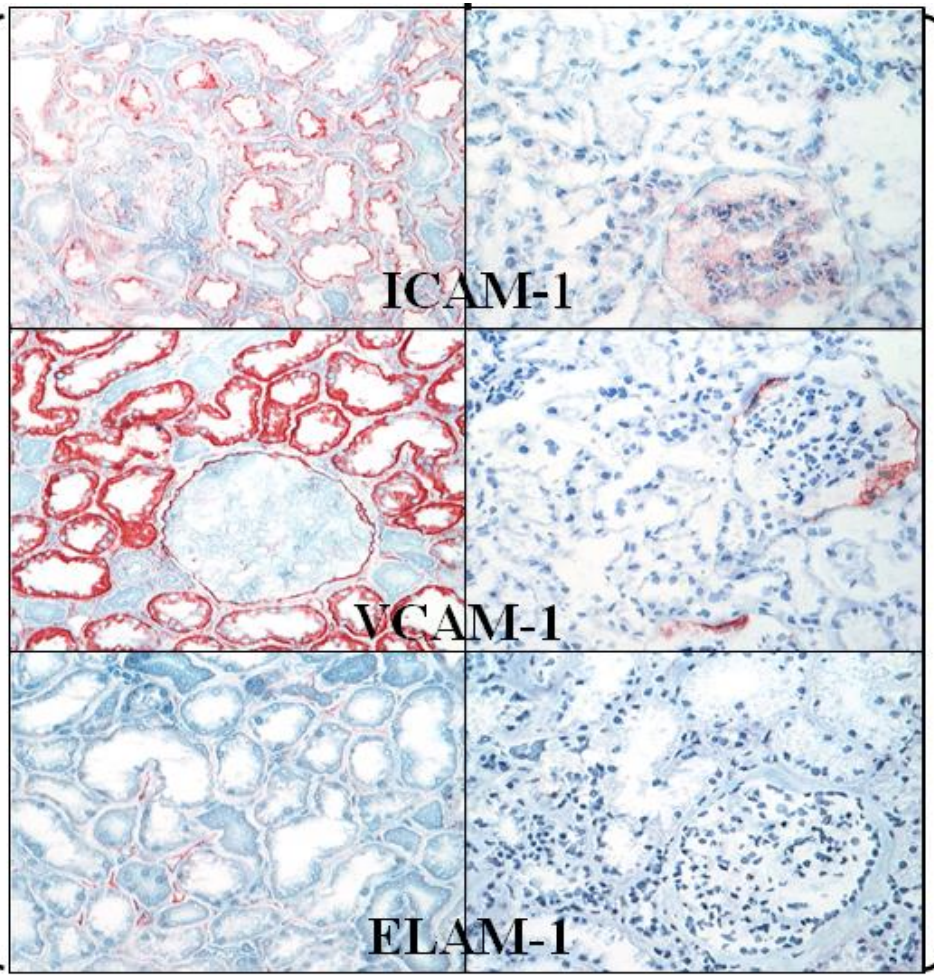
Histogenomics of allograft injury (n=82)



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

Inflammation in Deceased Donor Kidney Biopsies

DGF



PGF

Schwarz et al Transplantation 2007:71:1666-72

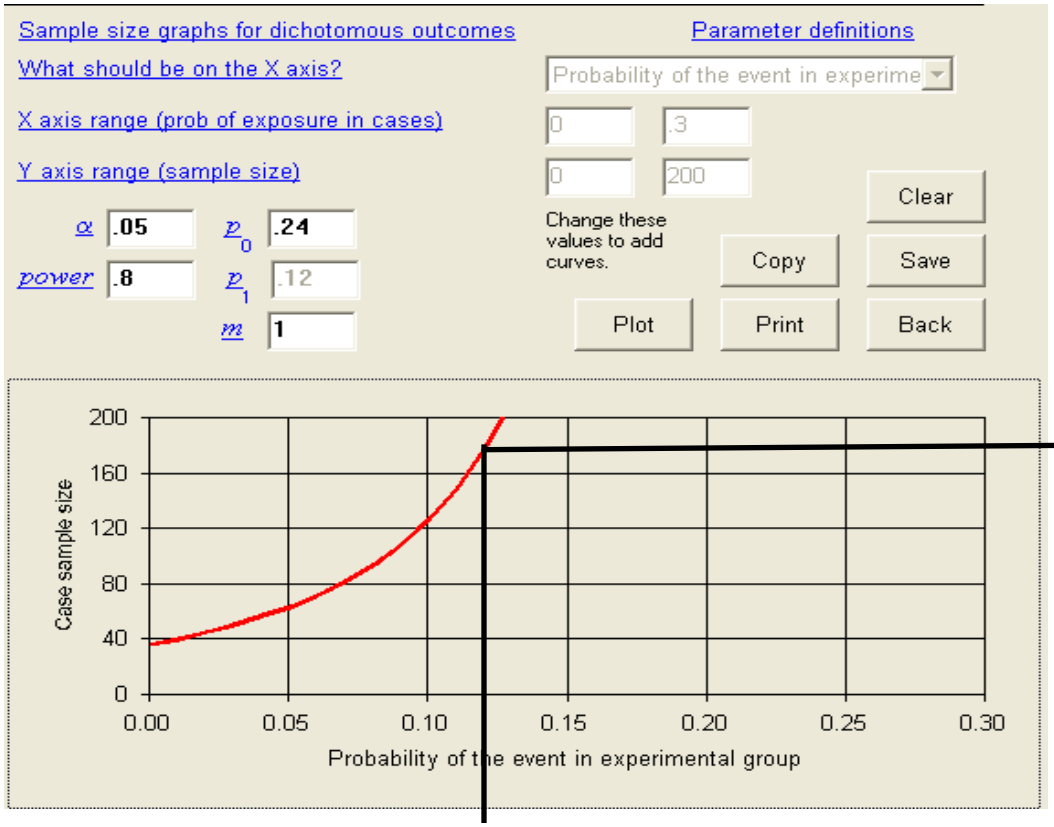
A Multicenter Double-Blinded RCT of Deceased Organ Donor Pre-Treatment with Corticosteroids for the Prevention of Postischemic Acute Renal Allograft Failure

Current Controlled Trials Registration #: ISRCTN78828338

Sponsor: Austrian Science Funds P15679, €350k

Kainz A et al. Ann Intern Med. 2010;153:222-230

Sample size estimation



12%

Event rate control group = 24%

Computed sample size to half event rate :

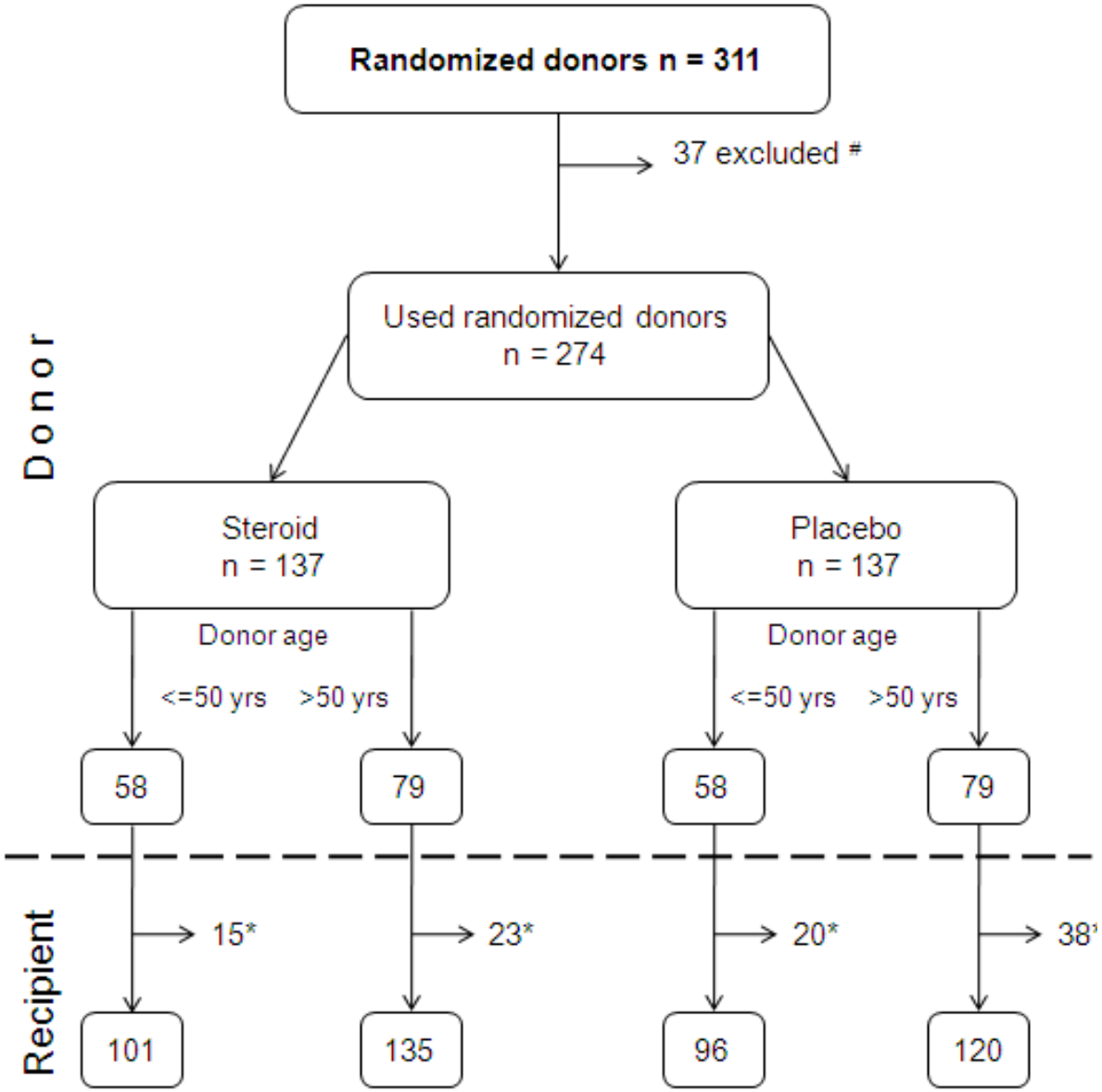
176

Donor sample size

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

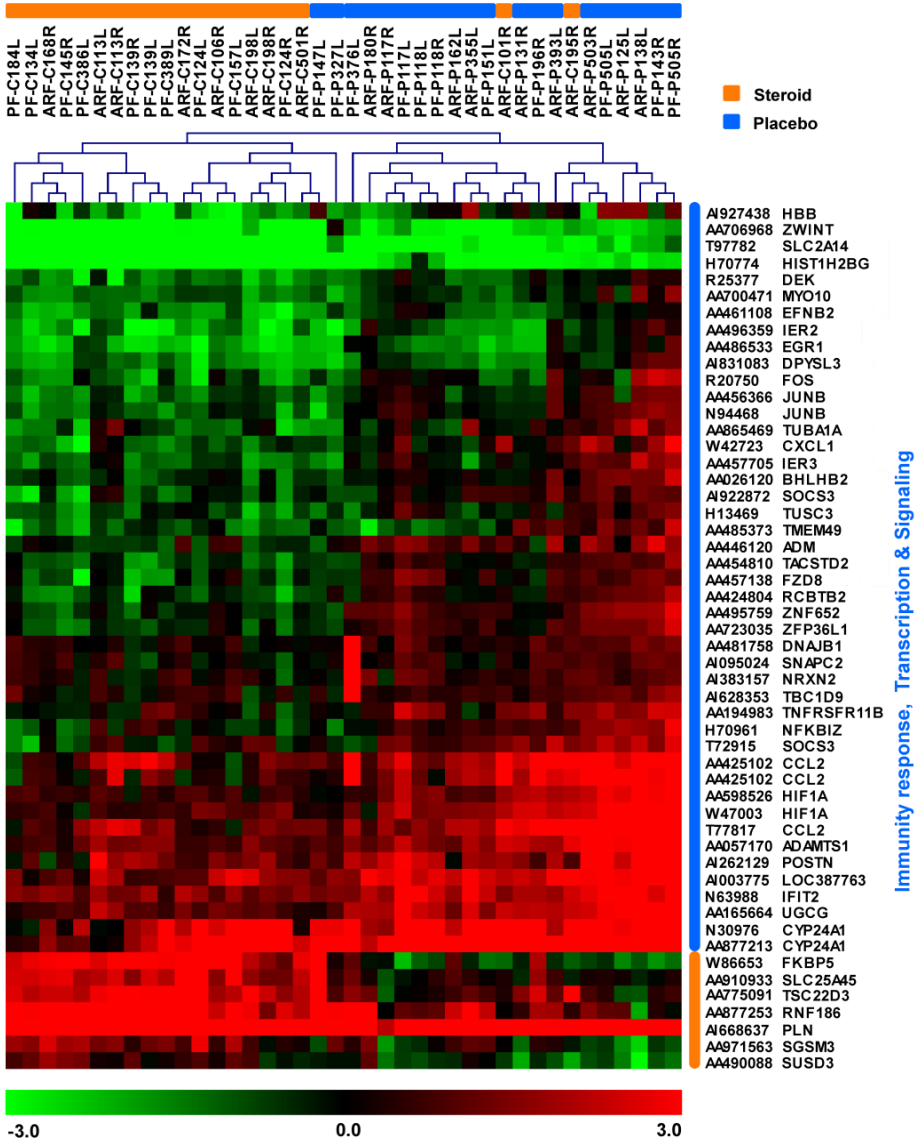
$=176(1/.92)^2=207$

Kainz A et al. Ann Intern Med. 2010;153:222-230



Kainz A et al. Ann Intern Med. 2010;153:222-230

Steroid treatment suppressed inflammation

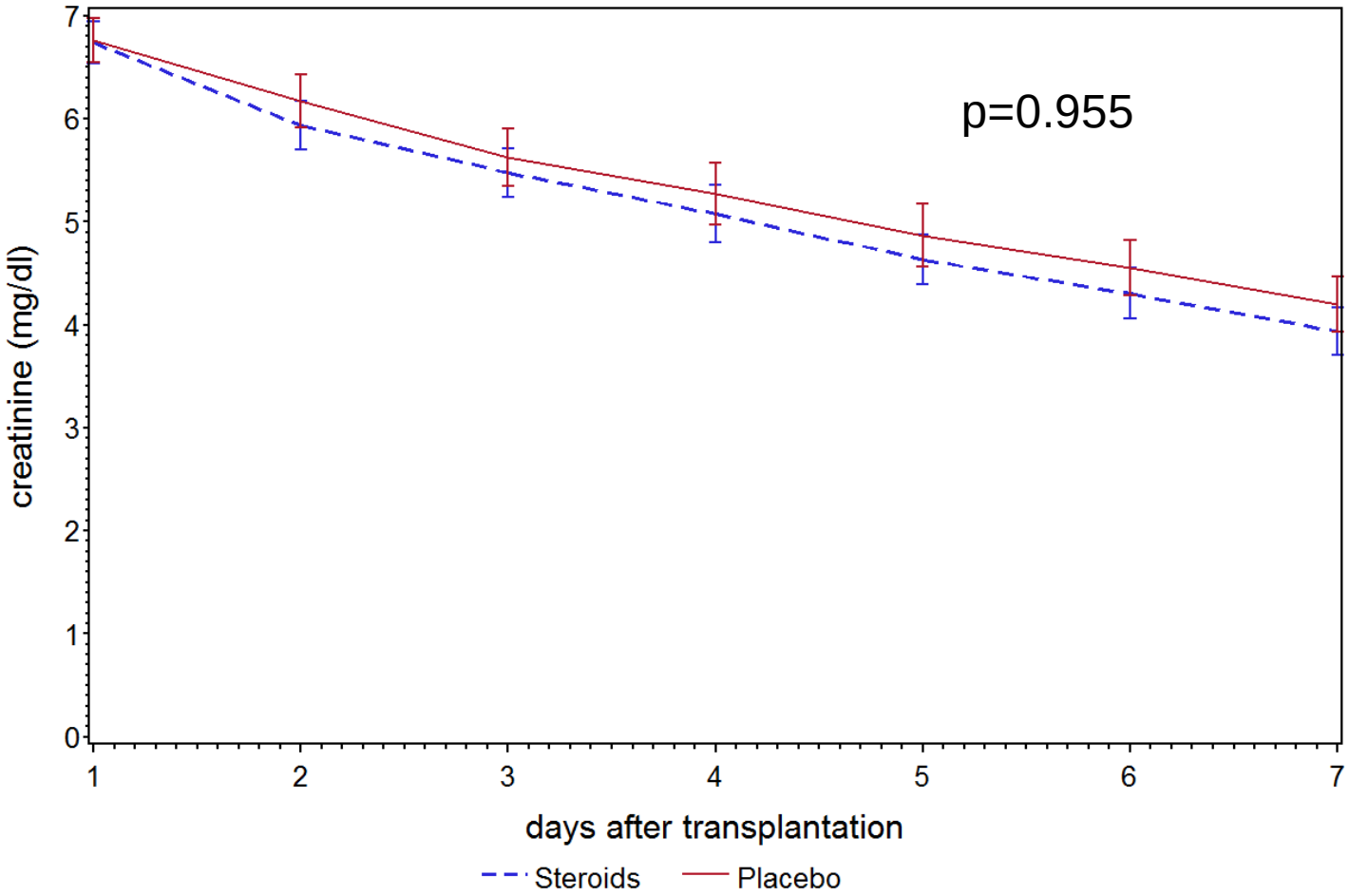


Primary study end point - DGF

	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

Kainz A et al. Ann Intern Med. 2010;153:222-230

Creatinine Trajectories



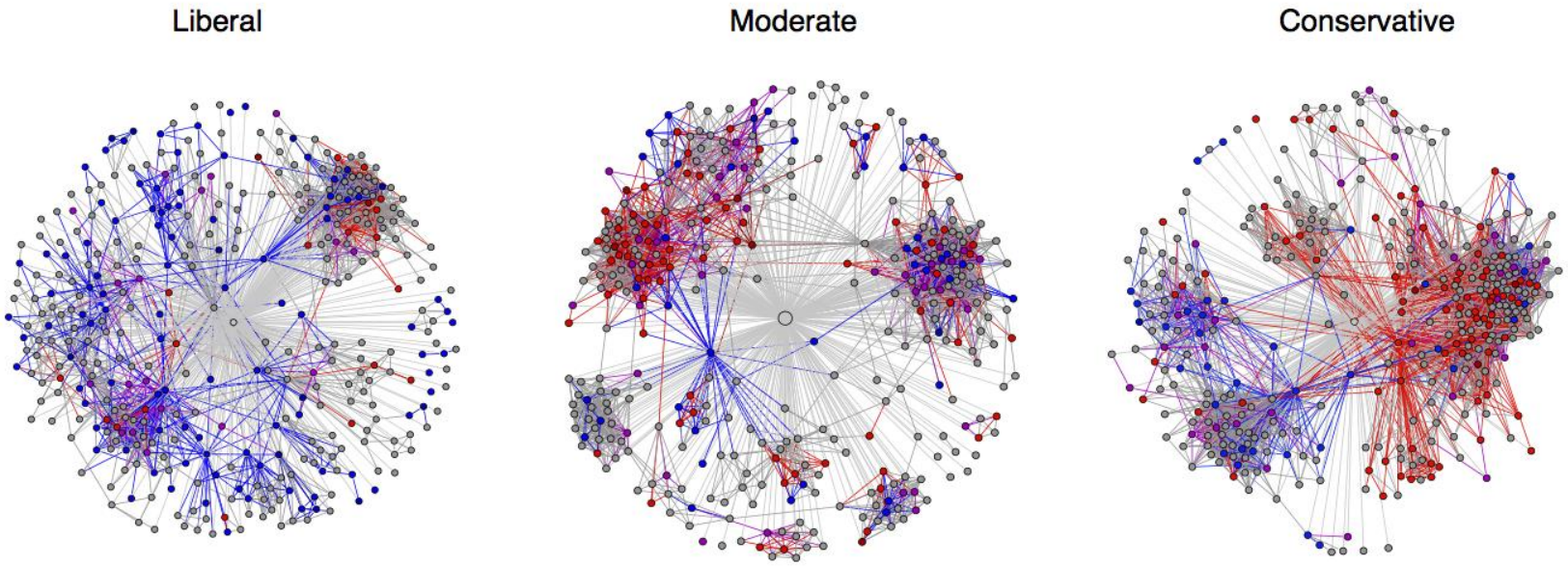
Kainz A et al. Ann Intern Med. 2010;153:222-230

Systems Biology – The concept of integration

Integration of information from different aspects (omics) to better characterize biological processes (interactome)

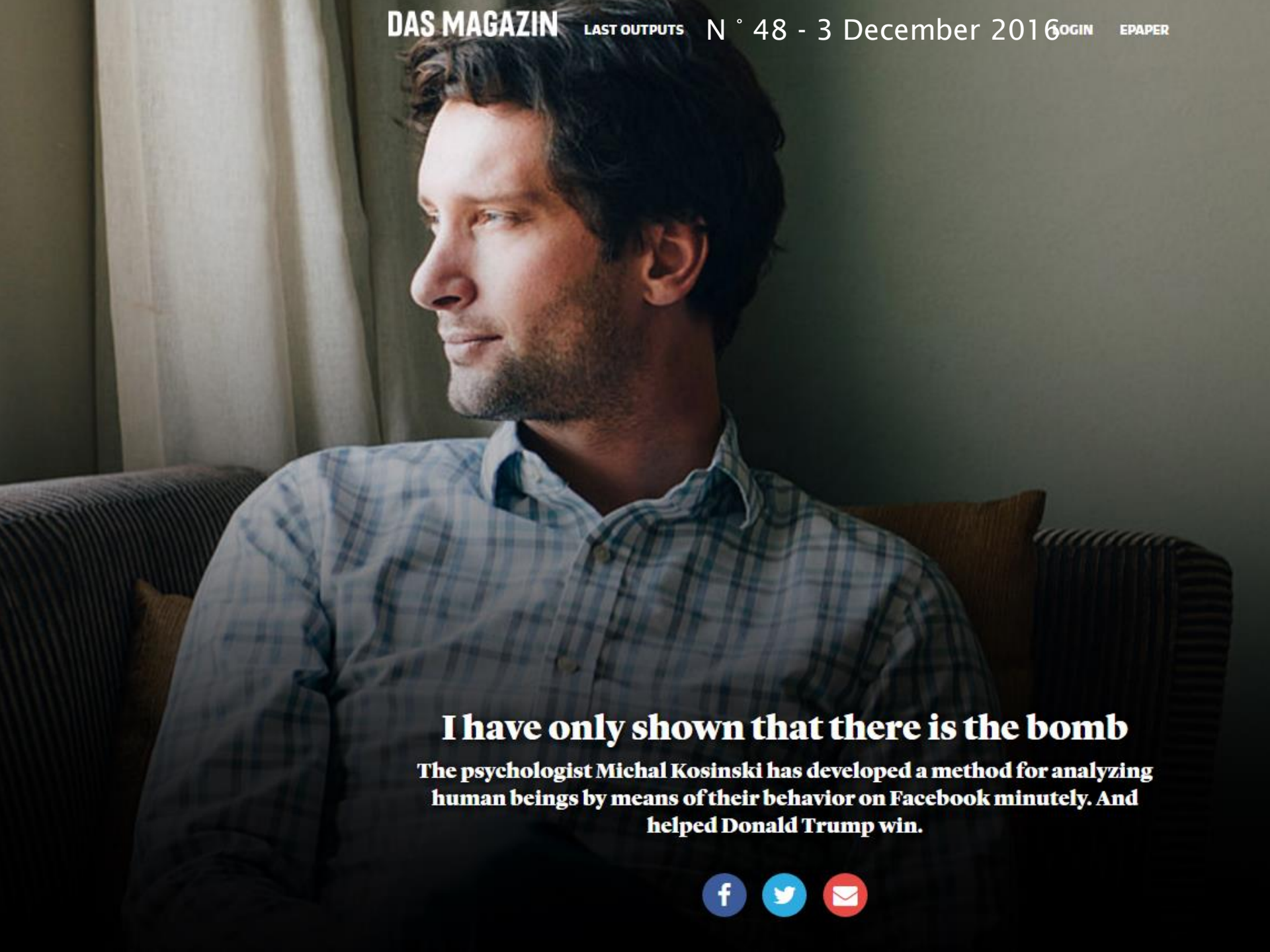
The Social Netwok, 10Mill US users and Indeology

Exposure to Diverse Information on Facebook



Echo Chambers

Bakshy E et al. Science. 2015 Jun 5;348(6239):1130-2



I have only shown that there is the bomb

The psychologist Michal Kosinski has developed a method for analyzing human beings by means of their behavior on Facebook minutely. And helped Donald Trump win.

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

→

BEAT DKD

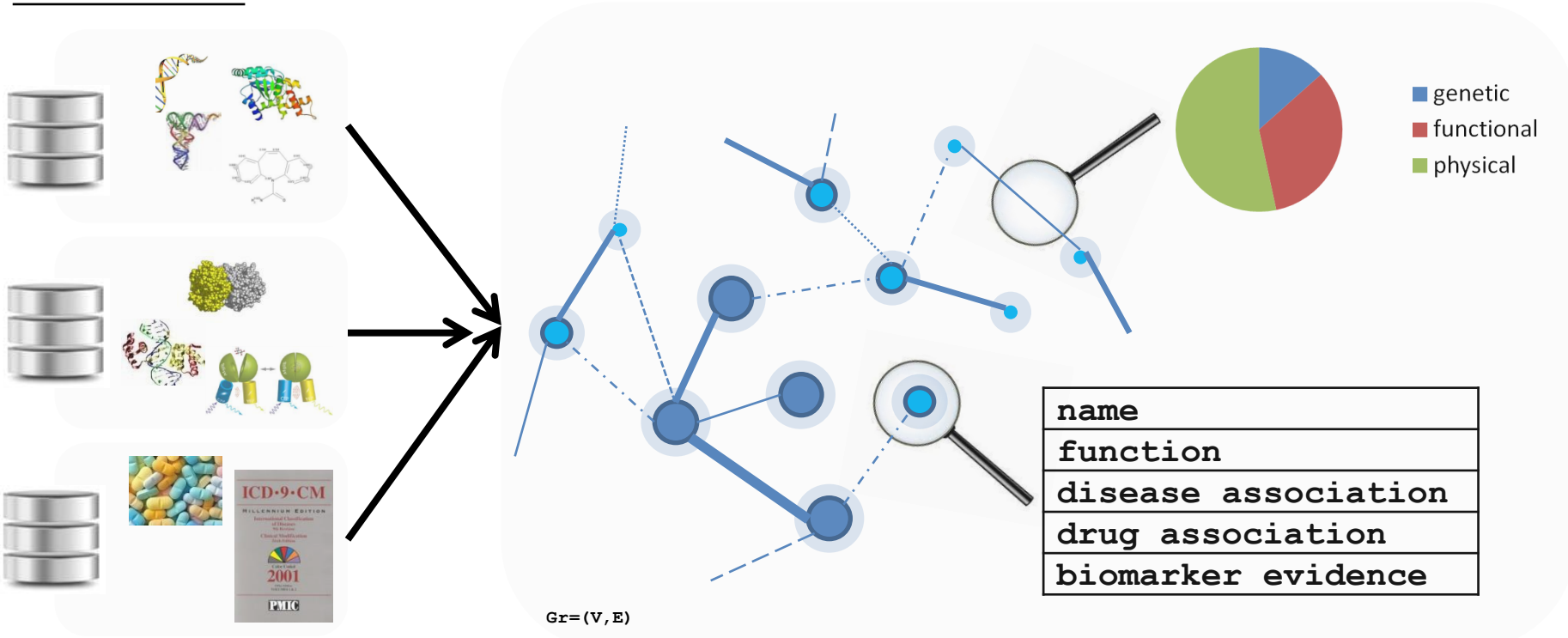
EU-FP7 Project - €16 Mio 2010-2015

EU-IMI-H2020 – €13 Mio 2016-2011

Integrated Analyses-
omicsNET, a full human proteome interaction network (19,263 vertices, 800,000 edges, 10 gigabyte)

consolidate nodes, relations, annotation

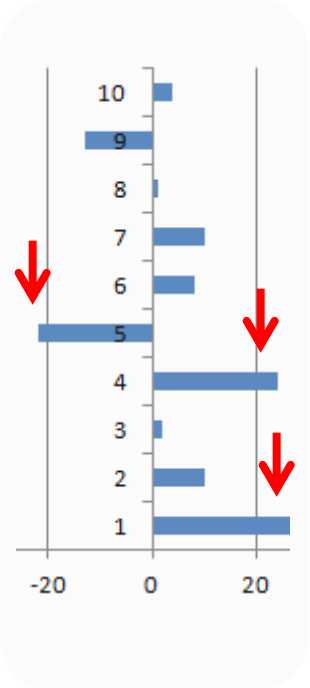
derive an annotated relations network



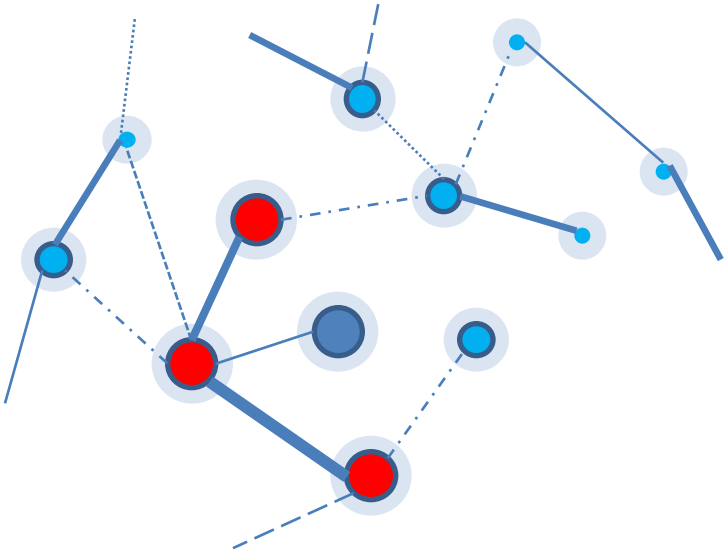
Bernthaler A et al.*Mol Biosyst* 2009; 5:1720-31,

Disease specific subgraphs and units

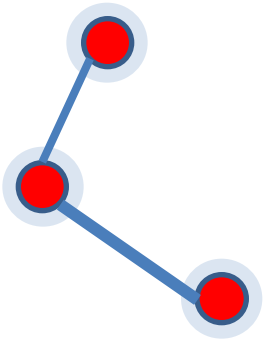
consolidate disease associated features



integrate on relations network



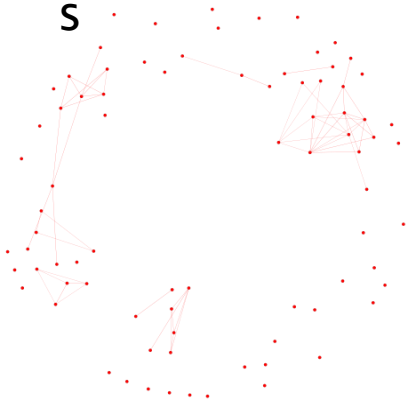
segment the network



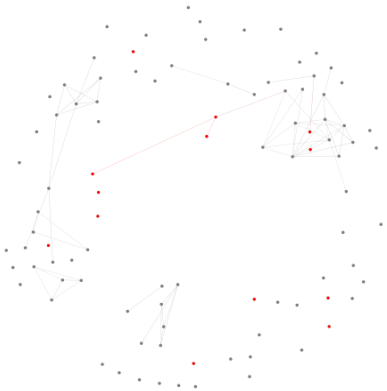
Bernthaler A et al.*Mol Biosyst* 2009; 5:1720-31,

POC - ARFspecific Network Definition

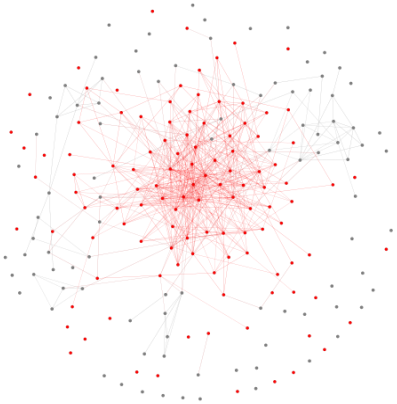
Metabolomics



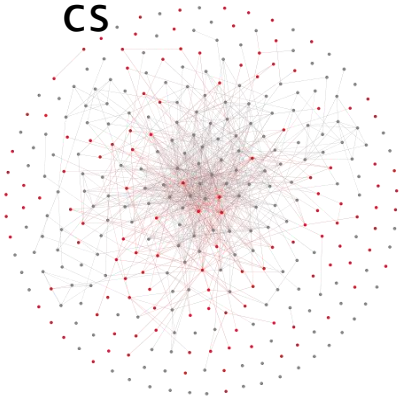
Proteomics



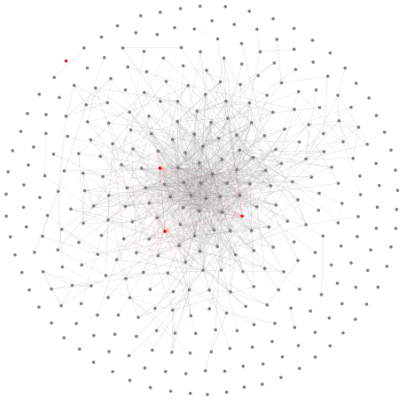
miRNA



Transcriptomics



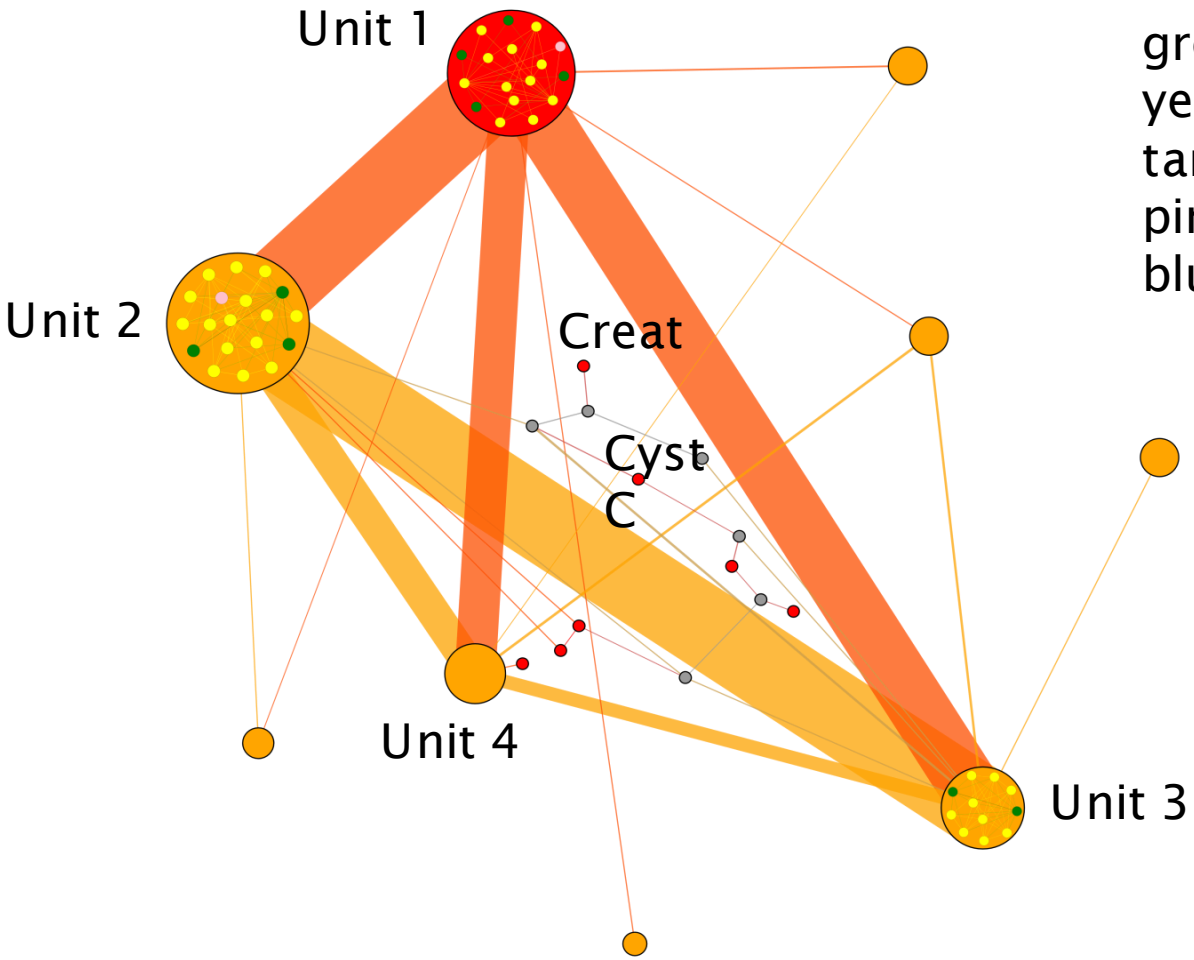
SNPs



Segmentation

Wilflingseder J et al. Am J Transplant 2013

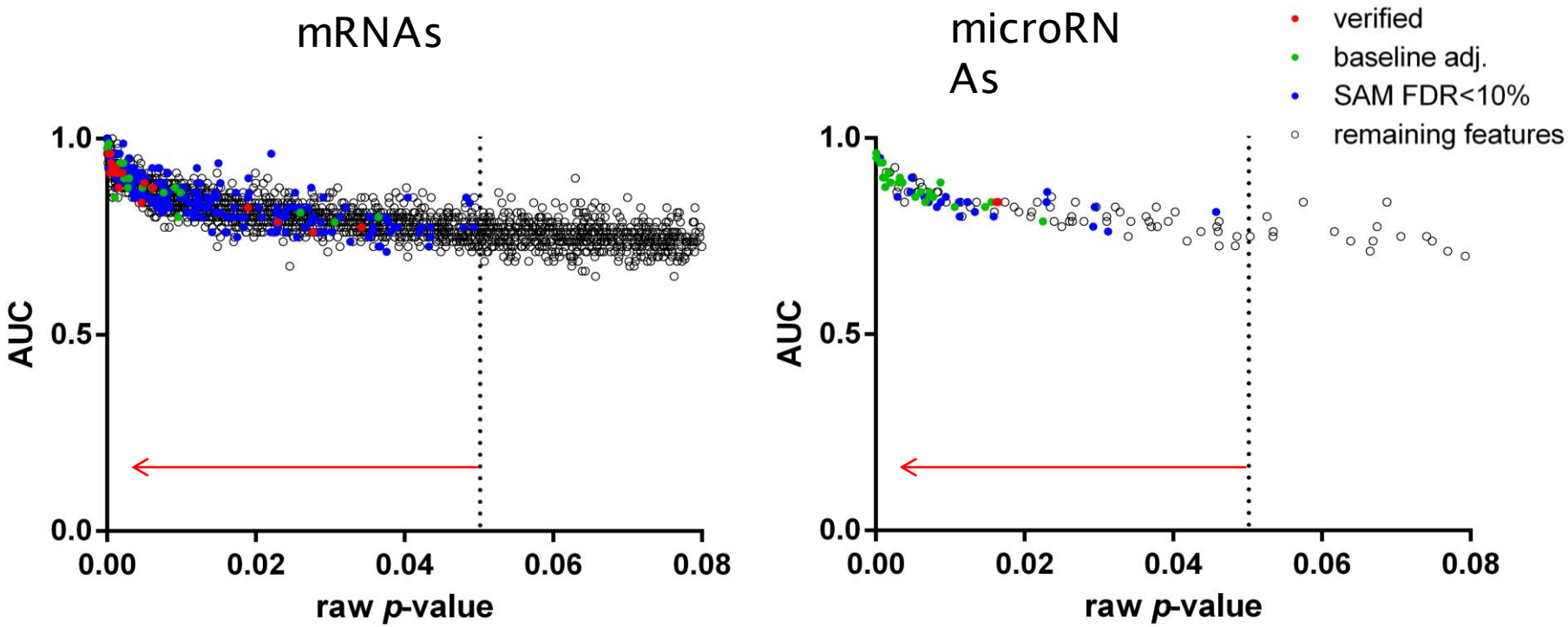
ARF Biomarkers



green – mRNA
yellow – miRNA targets
pink – SNPs
blue - proteomics

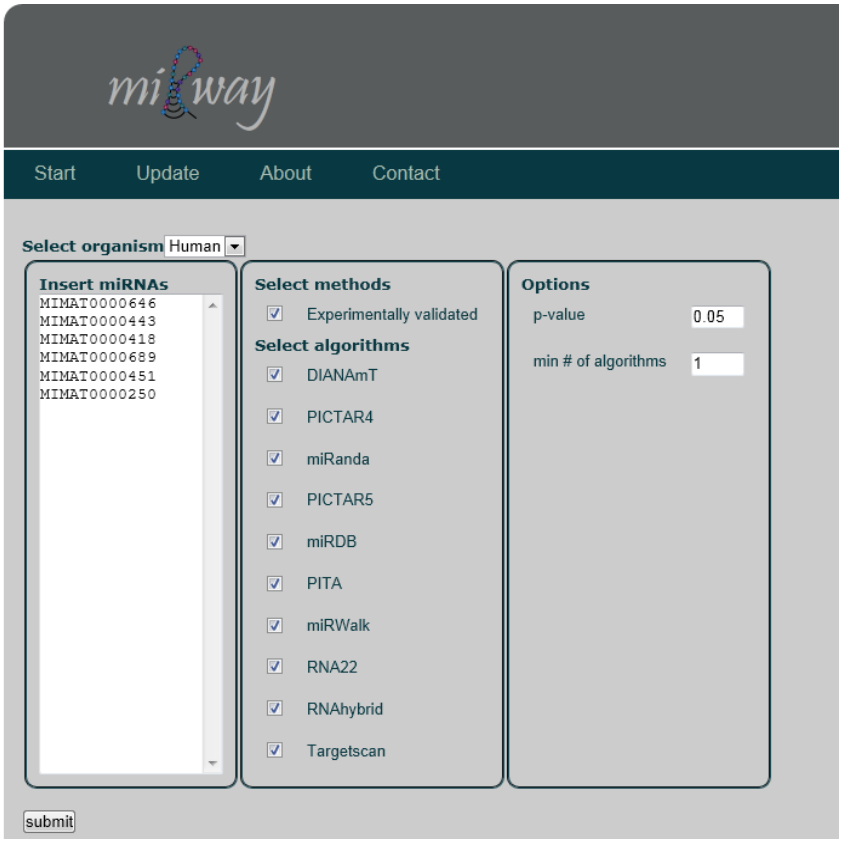
Wilflingseder J et al. Am J Transplant 2013

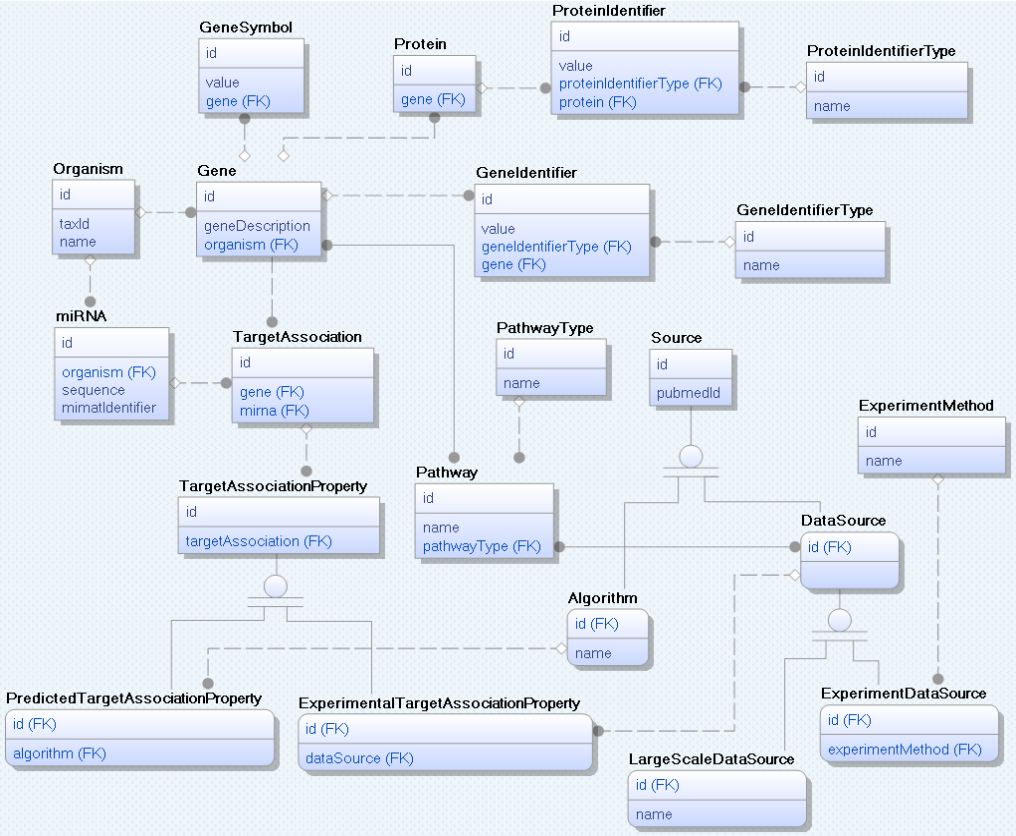
Experimental discrimination of ARF and PGF



Wilflingseder J et al. PLoS One. 2014 Aug 5;9(8):e104164

miRNA target prediction tool



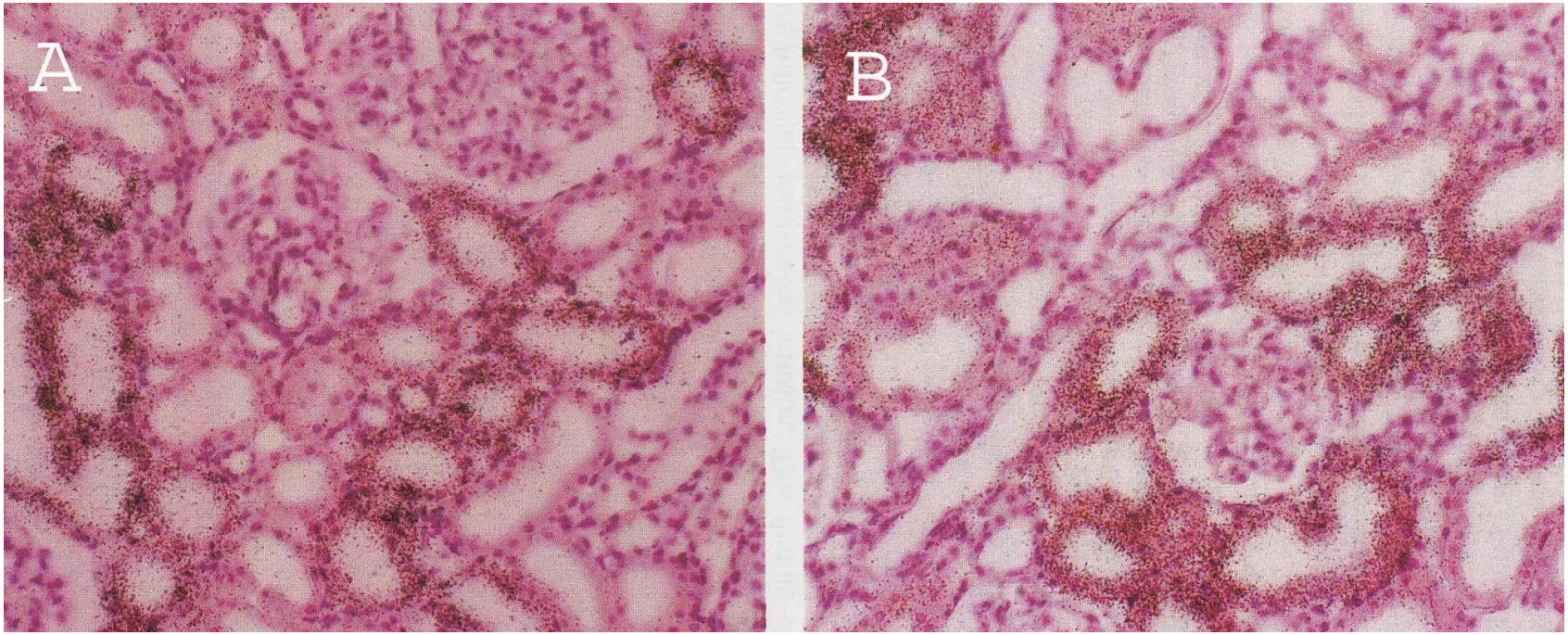


Ivcevic S, Stütz C et al. 2014

miR-182 targets (yellow) in the ARF Network

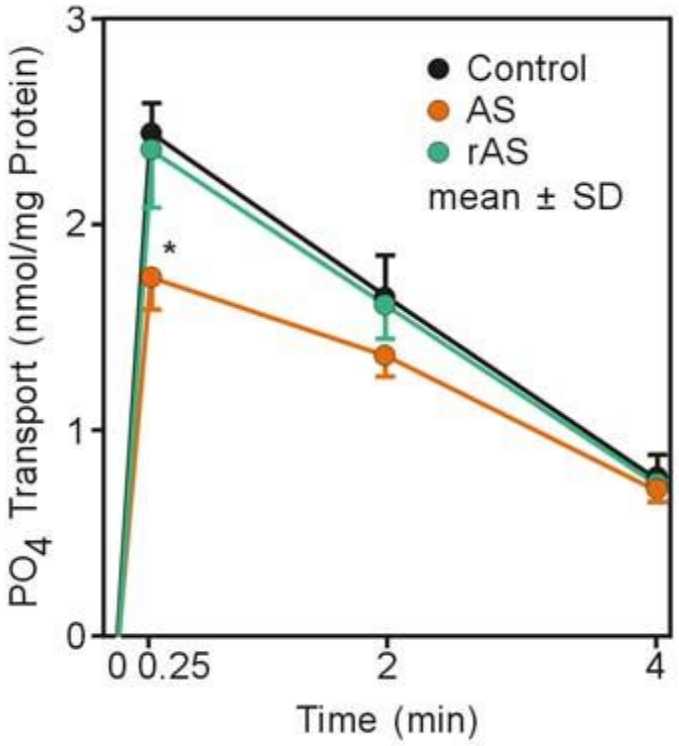
Wilflingseder J et al. Transplantation 2013; 95(6):835-41.

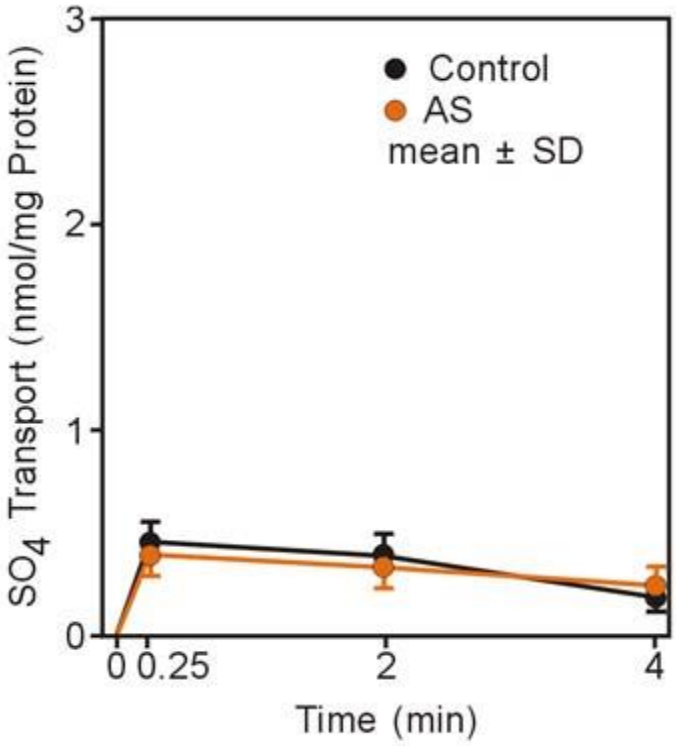
Antisense DNA/siRNA *in vivo* Kinetik



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

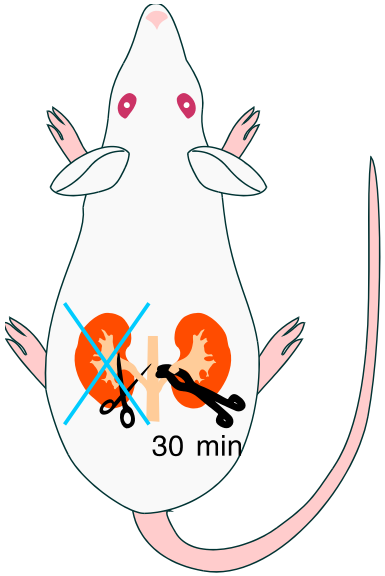
POC: In vivo Blockade von NaPi-2 mit antisense DNA

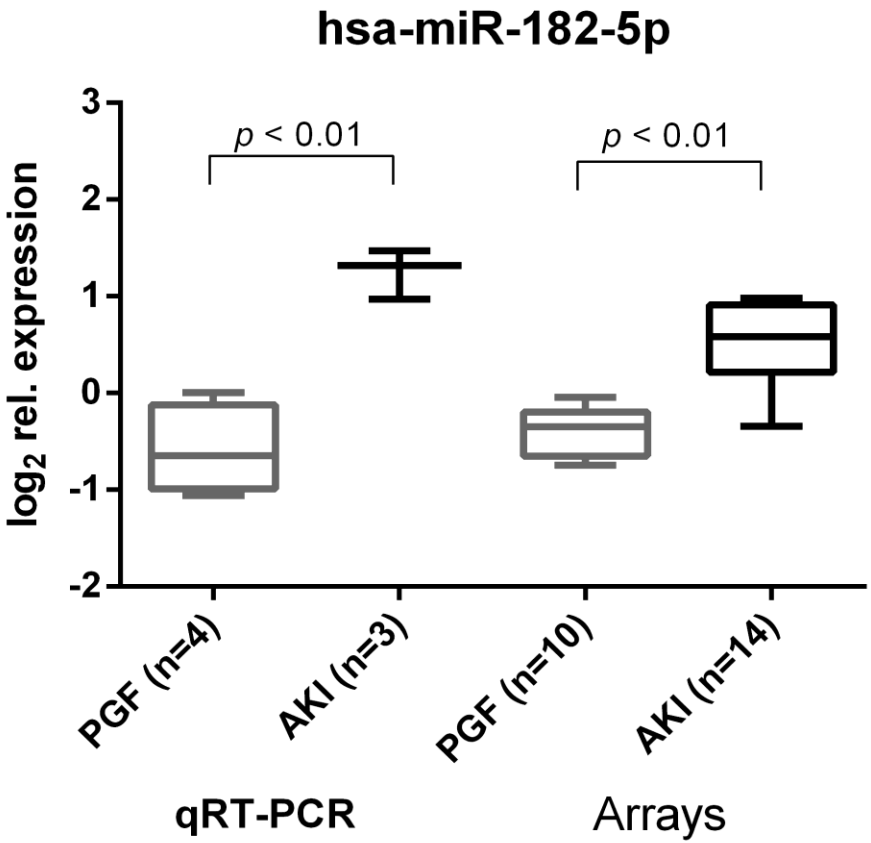




Oberbauer R et al. PNAS, 1996, 93:4903-4906

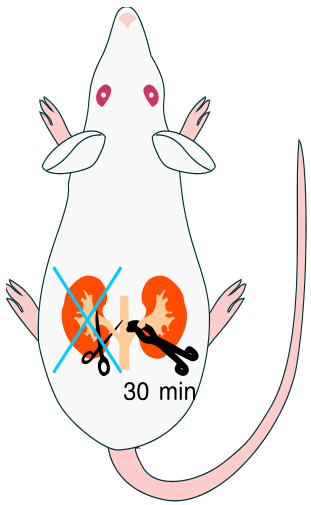
POC: miR182 regulation in ARF

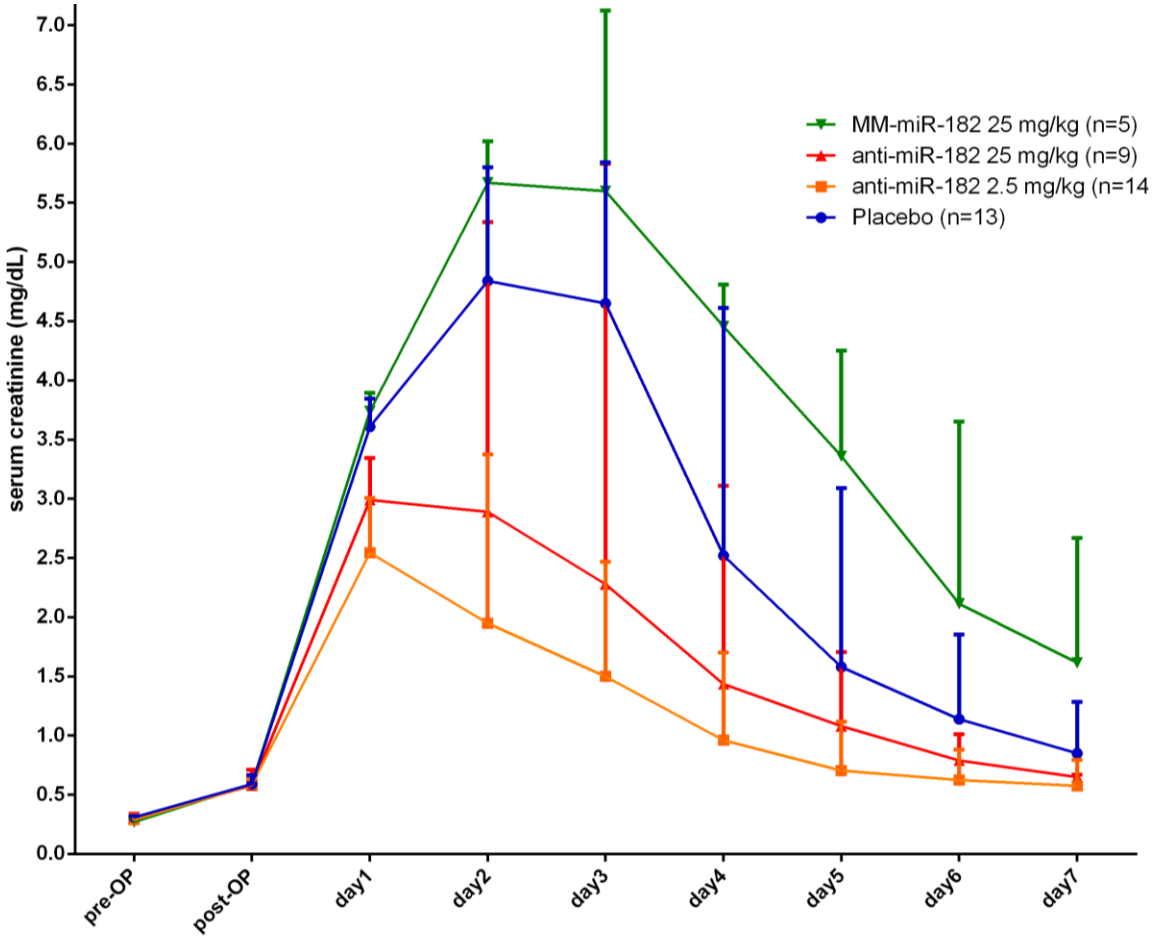




Wilflingseder J et al. Am J Pathol. 2017 Jan;187(1):70-79

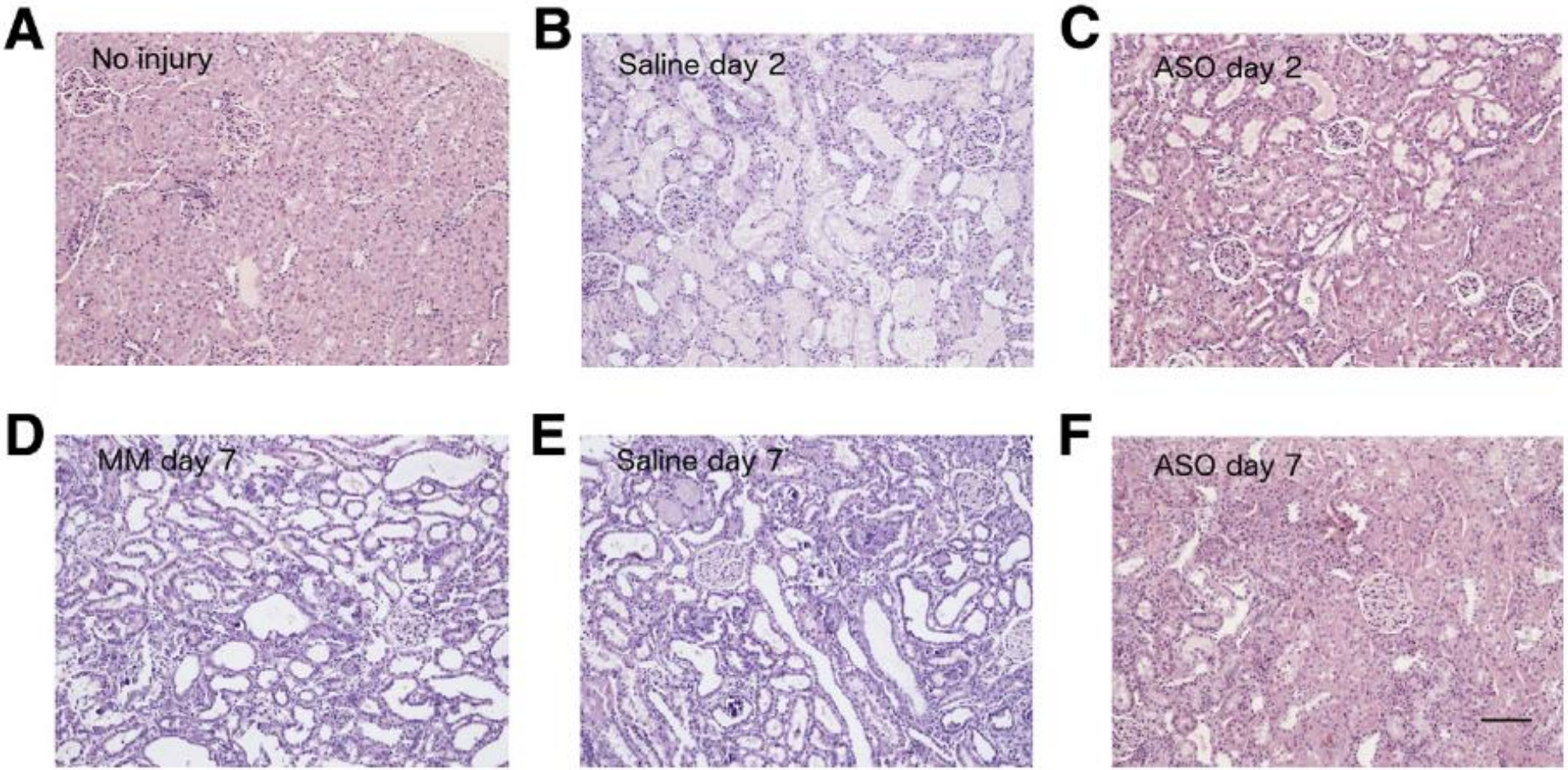
antimiR-182 ameliorated ARF





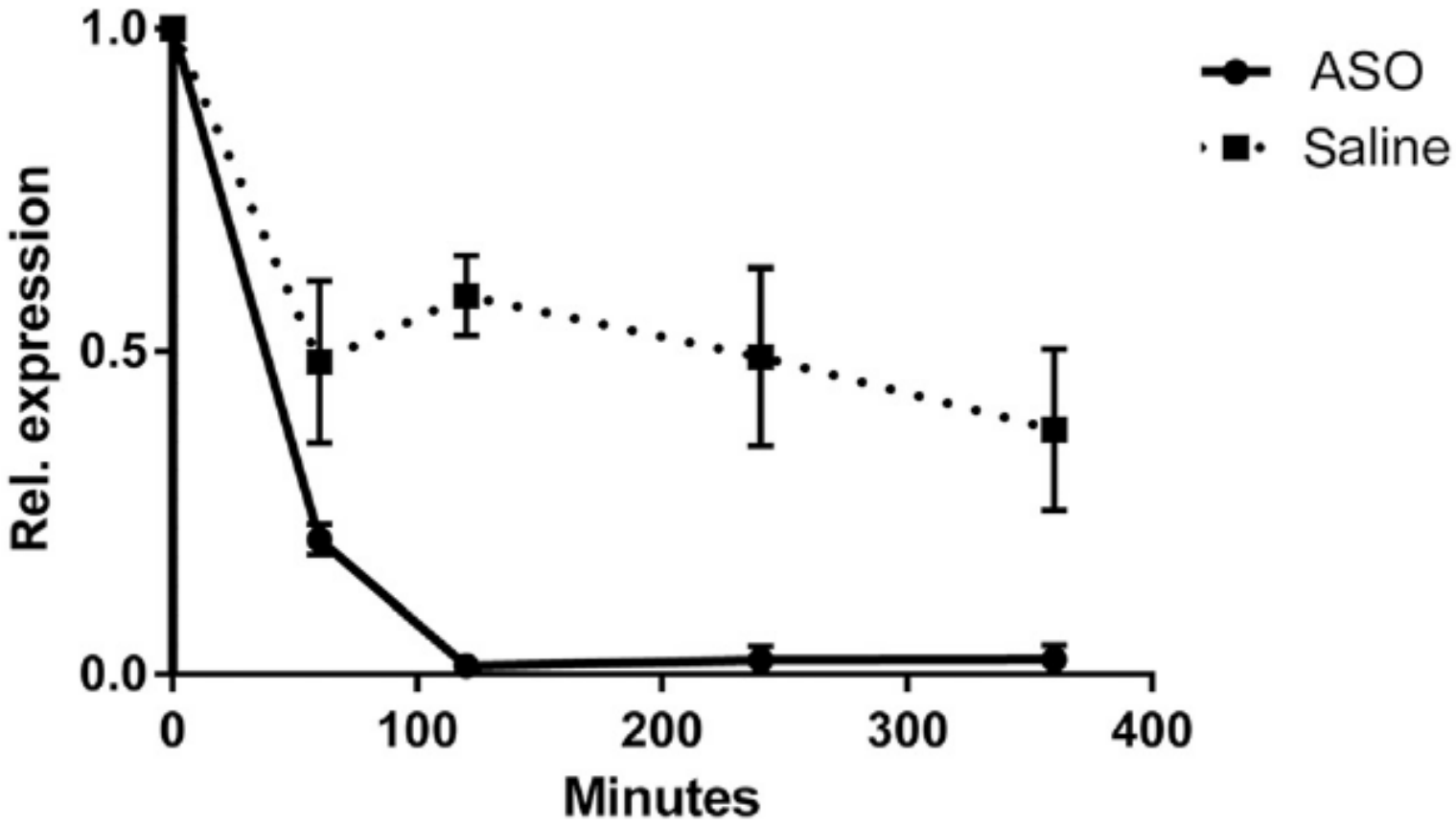
Wilflingseder J et al. Am J Pathol. 2017 Jan;187(1):70-79

Histology of ASO vs control rats



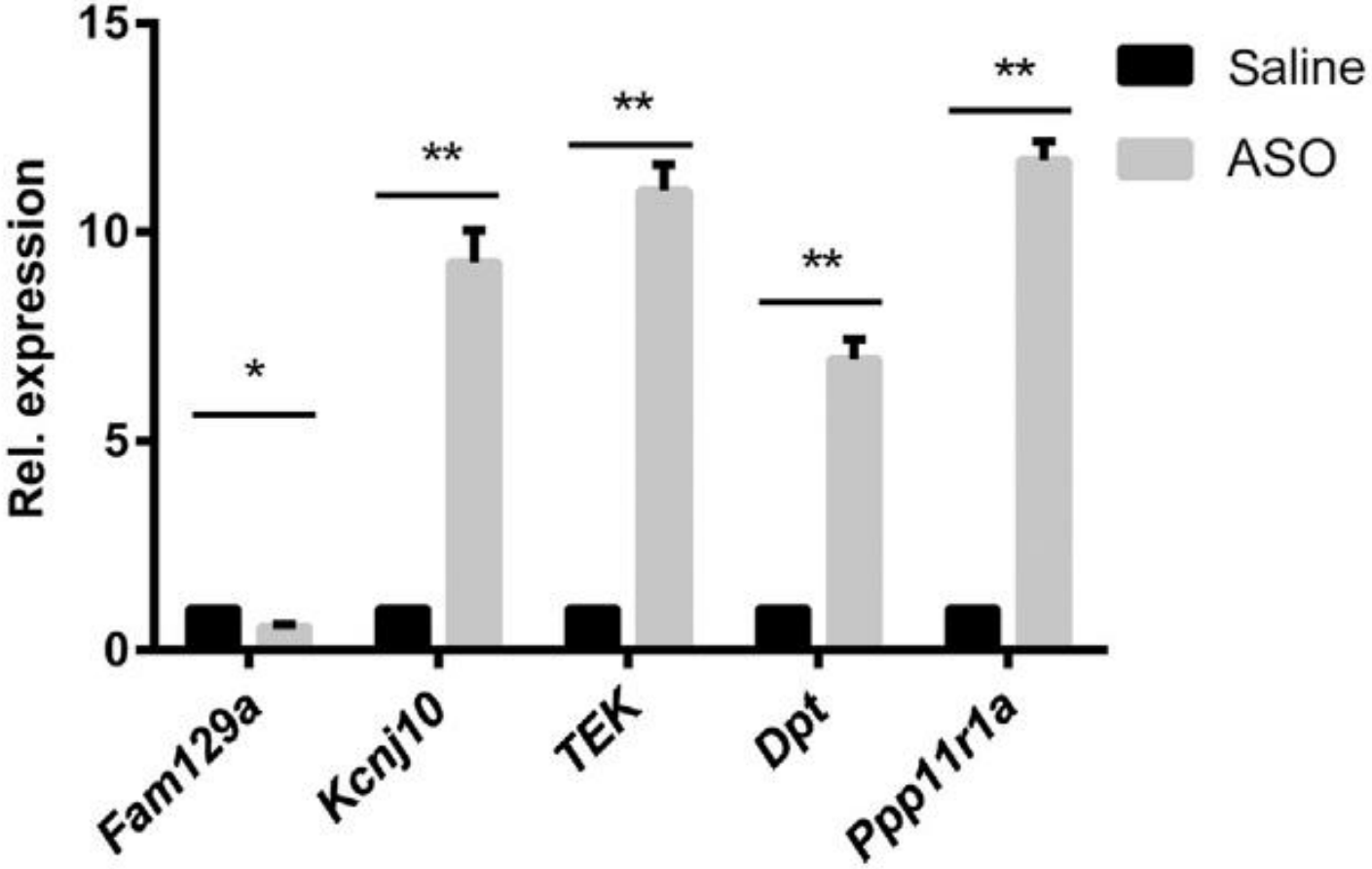
Wilflingseder J et al. Am J Pathol. 2017 Jan;187(1):70-79

Pig donor kidney *ex vivo* machine perfusion with antimiR-182



Wilflingseder J et al. Am J Pathol. 2017 Jan;187(1):70-79

Expression of various miR-182-5p targets of pig donor kidney by *ex vivo m*achine perfusion with antimiR-182 (ASO)



Wilflingseder J et al. Am J Pathol. 2017 Jan;187(1):70-79

Lifeport – *ex vivo* Donor kidney prfusion IRB Nr 1443/2012

Organ Recovery
systems

Organ Recovery Systems
DaVincilaan 2 Box 6
1935 Zaventem
Belgium
Tel 32 (0)2 715.0000
Fax 32 (0)2 715.0009
pdemuylder@organ-recovery.com

To the
Austrian Science Funds – FWF
Sensengasse 1, A-1090 Wien
T +43-1-505 67 40 F +43-1-505 67 39
office@fwf.ac.at - www.fwf.ac.at)

May 9, 2012

Re: Letter of intent to collaborate on the anti miR-182 ARF project submitted by Dr. Rainer Oberbauer

Dear Madam, Sir,

We are very pleased to inform you that we are willing to support Dr. Oberbauer's proposed study about the treatment of discarded human kidneys with antisense miR-182. For this purpose a

MicroRNA-122 in Hepatitis C - GT1

Janssen HLA et al. N Engl J Med 2013;368:1685-94.

CONCLUSIONS

The use of miravirsen in patients with chronic HCV genotype 1 infection showed prolonged dose-dependent reductions in HCV RNA levels without evidence of viral resistance. (Funded by Santaris Pharma; ClinicalTrials.gov number, NCT01200420.)

Targeting Therapeutic Oligonucleotides

Arthur A. Levin, N Engl J Med. 2017 Jan 5;376(1):86-88.

Ultimately, the success of targeted delivery approaches will depend on the rates of internalization and the specific trafficking of the receptor-bound conjugate within cells. However, the existing data indicate that sufficient quantities of oligonucleotide drug can be internalized to produce meaningful reductions in gene expression. These results, taken together with the progress from the ongoing clinical studies with GalNAc-conjugated oligonucleotides,[7,8] show that oligonucleotide-based drugs are improving with targeted delivery.

Summary

- Tools and technology are available to model disease pathophysiology, e.g. post TX ARF
- Long way from molecular signatures to predictive and therapeutic biomarkers/leads
- Consortial effort (LS, IT, Maths, etc)
- ARF/DGF might be an optimal POC model in TX

Rainer Oberbauer – Nep

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// Latest Publications:

136. Positioning of tacrolimus for the treatment of diabetic nephropathy based on computational network analysis. Plos One 2016 (in press)

Aschauer C, Perco P, Heinzel A, Sunzenauer J, Oberbauer R

VIEW PDF

135. Steroid withdrawal after renal transplantation: a retrospective cohort study. BMC Medicine 2016 (in press)

Haller M, Kammer M, Kainz A, Bear HJ, Heinze G, Oberbauer R

VIEW PDF

134. Systems biology derived biomarkers to predict progression of renal function decline in type 2 diabetes mellitus. Diabetes Care 2016 (in press)

Mayer G, Heerspink HL, Aschauer C, Heinzel A, Heinze G, Kainz A, Sunzenauer J, Perco P, de Zeeuw D, Rossing P, Pena M, Oberbauer R

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