TRANSPLANTATIE: WAT WE HEBBEN GELEERD OVER DE UITDAGINGEN VAN MORGEN?

Ben SPRANGERS

08-03-2016

Overview

- Transplantation in 2016
- Non-invasive diagnosis - biomarkers
- Humoral rejection takes center stage
- Don’t loose sight of the basics
  - Non-adherence
  - Machine perfusion
  - Hypothermia
  - Anastomosis time
  - Better immunosuppressive drugs
- Alternatives for classic kidney transplantation

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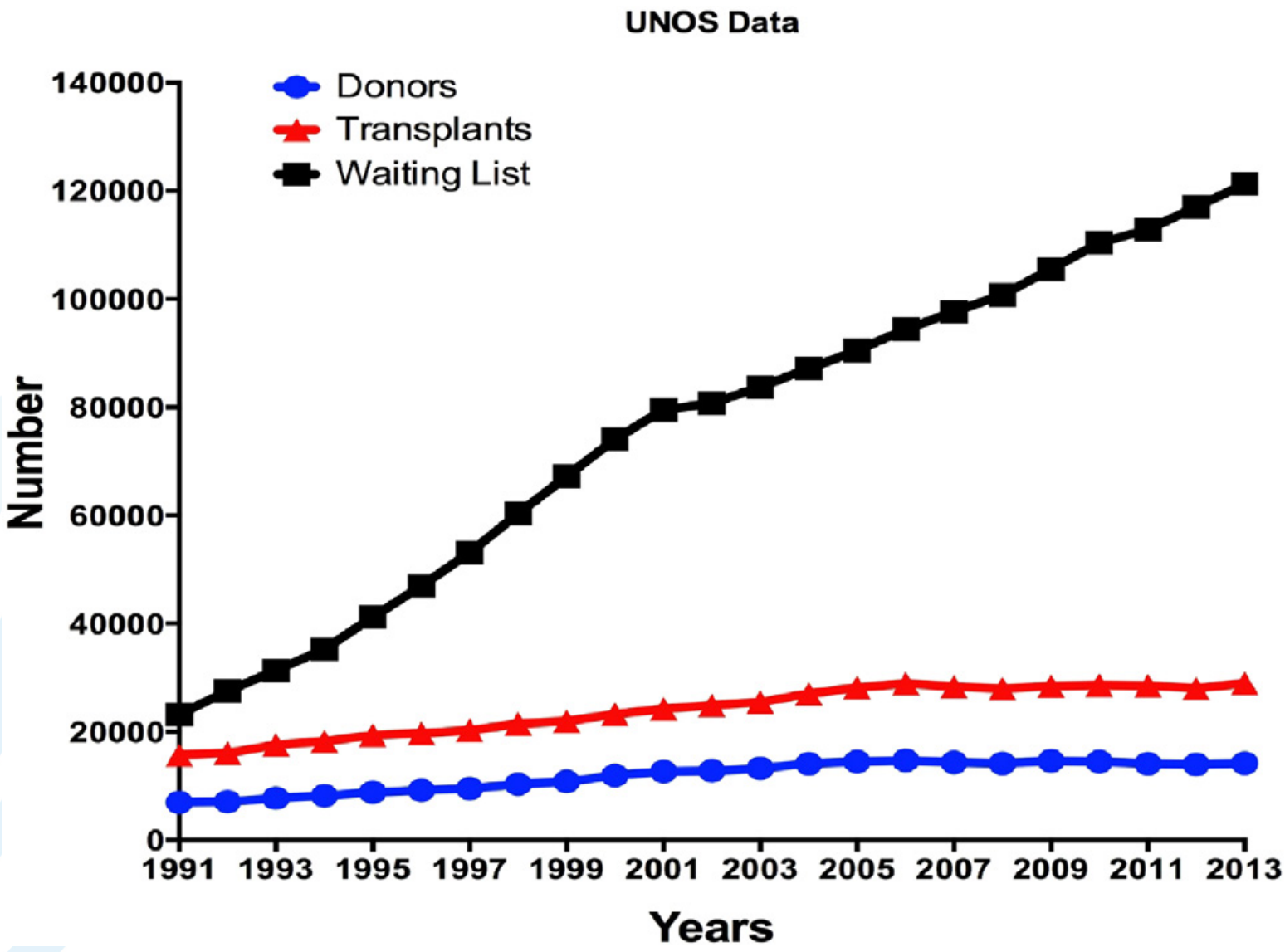
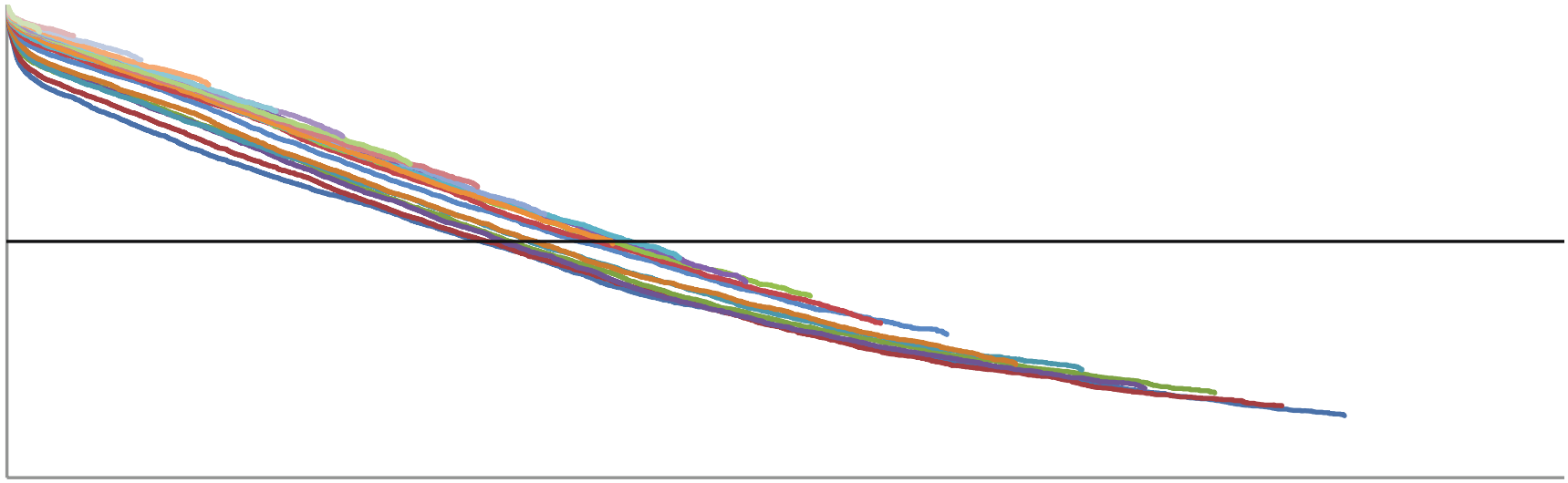
Transplantation in 2016



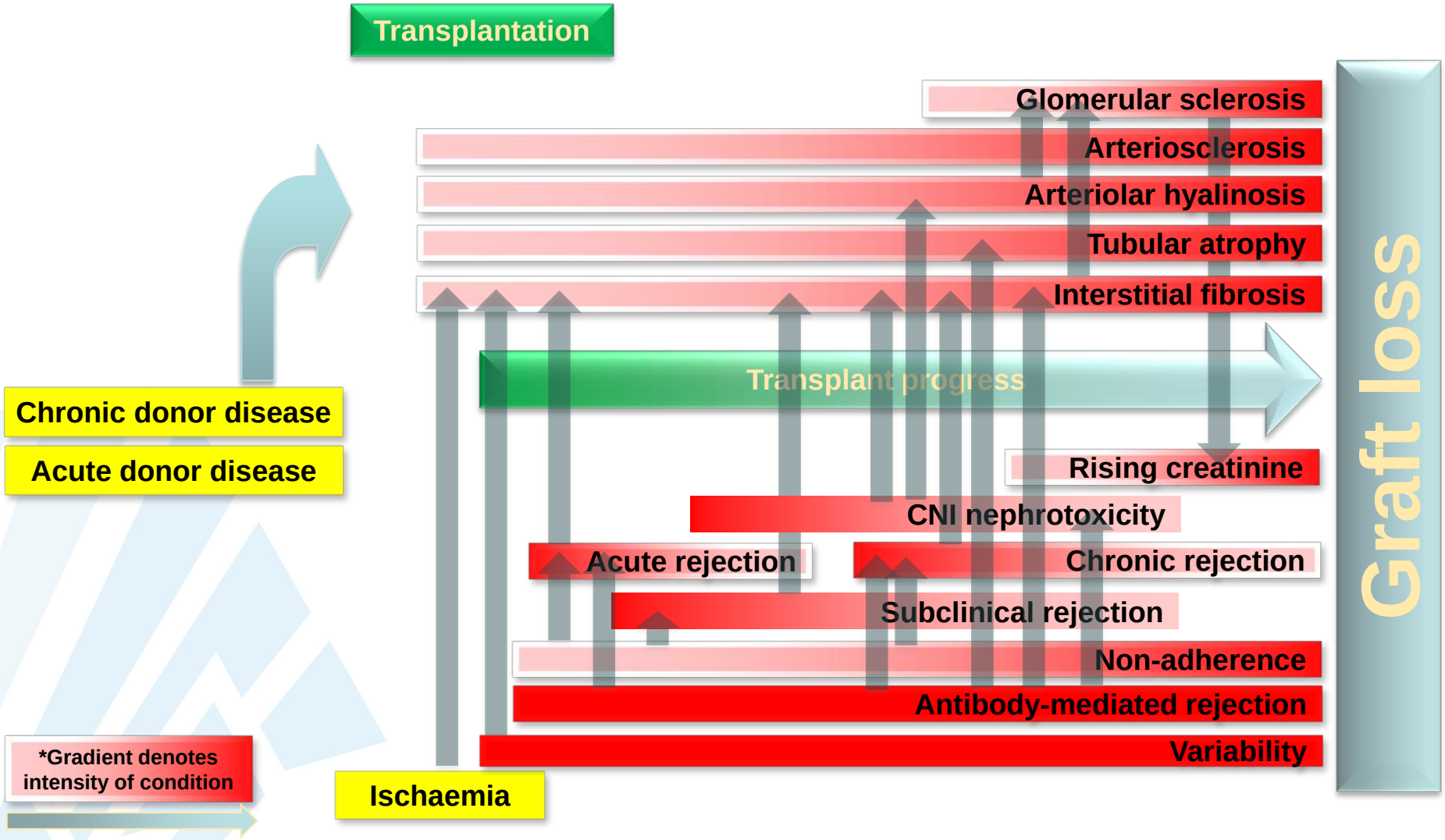
UNOS data

Transplantation in 2016



Lamb KE et al. Am J Transpl 2011;11:450-462.

Transplantation in 2016



From transplantation to graft loss

Adapted from Chapman JR et al. *J Am Soc Nephrol* 2005;16:3015−3026.
Nankivell BJ, Kuypers DRJ. *Lancet* 2011;378:1428–1437.

Transplantation in 2016

Panel 1: **Causes and risks of graft failure**

Non-immune donor risks

- Deceased donor kidney, non-heart beating donor kidney
- Donor older than 60 years, female donor sex, donor vascular disease or vascular comorbidity—ie, expanded criteria donor
- Ischaemia-reperfusion injury and long ischaemia times
- Delayed graft function

Non-immune recipient risks and causes

- Female sex, size mismatch (especially paediatric recipients), obesity
- Ascending urinary tract infection and graft pyelonephritis
- Transplant ureteric obstruction
- Polyoma (BK) virus nephropathy
- Calcineurin inhibitor nephrotoxicity
- Recurrent renal disease or de novo glomerulonephritis
- Hypertension, hyperlipidaemia, smoking, proteinuria
- Pre-existing or post-transplantation diabetes

Alloimmune factors

- Child or adolescent recipient, ethnicity with altered disposition of immunosuppressive agents
- Variable medication trough concentrations (from malabsorption or non-compliance)
- Recipient's genetic alloimmune and inflammatory response
- Histoincompatibility (HLA mismatches), recipient presensitisation (panel reactive antibodies), or donor specific antibodies
- Acute rejection that is severe, steroid-resistant, vascular, antibody-mediated, or late occurring
- Subclinical rejection, chronic T-cell mediated rejection, late de novo anti-HLA antibody formation (donor-specific antibodies), and chronic antibody-mediated rejection with transplant glomerulopathy
- Non-adherence to treatment

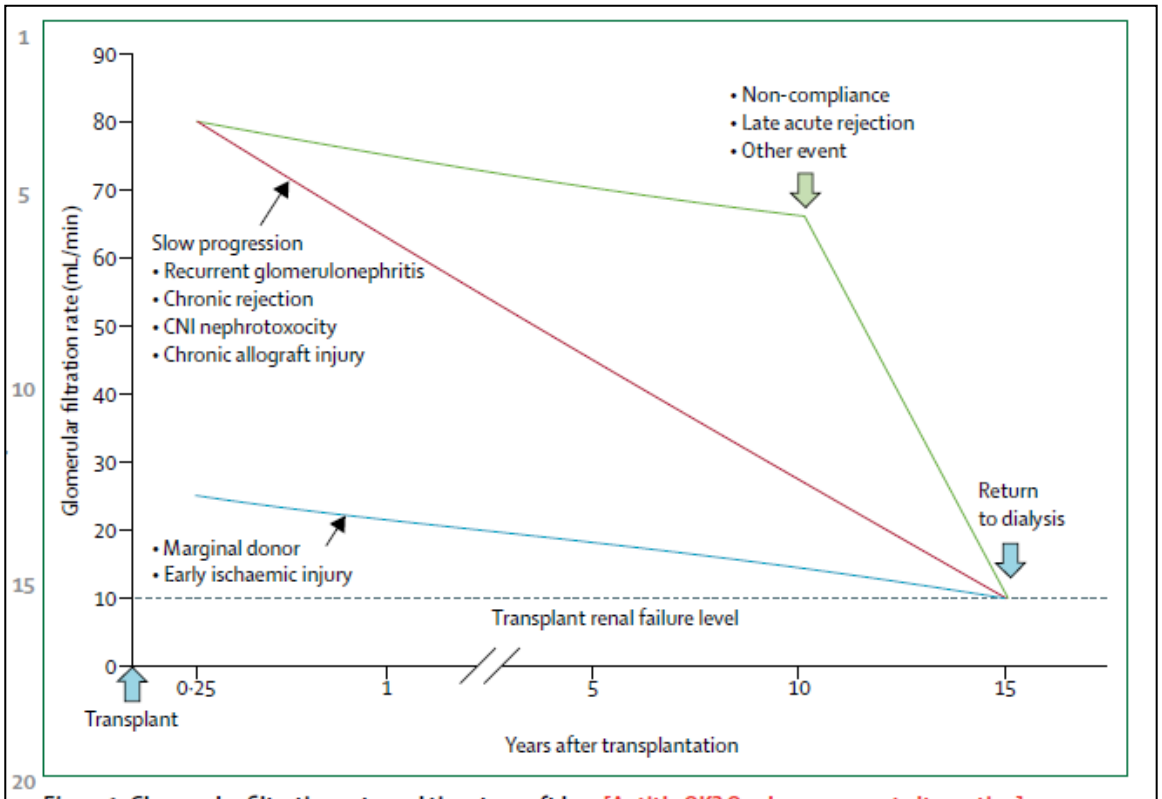
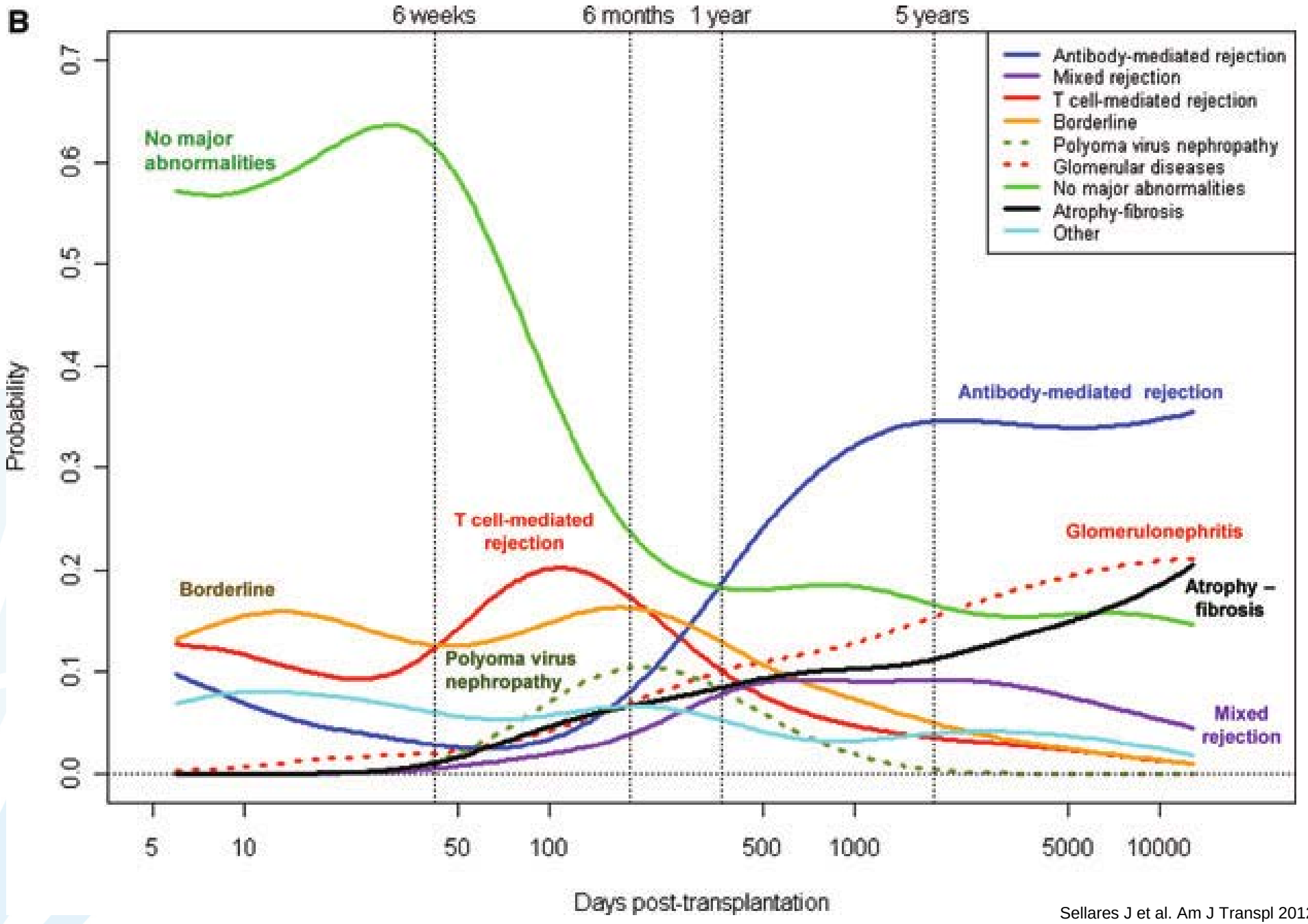


Figure 1: **Glomerular filtration rate and time to graft loss** [A: title OK? Or please suggest alternative]
Time to graft failure can be projected from the baseline rate (intercept, determined by donor quality and early events) and rate of loss (slope, indicating ongoing injury). CNI=calcineurin inhibitor.

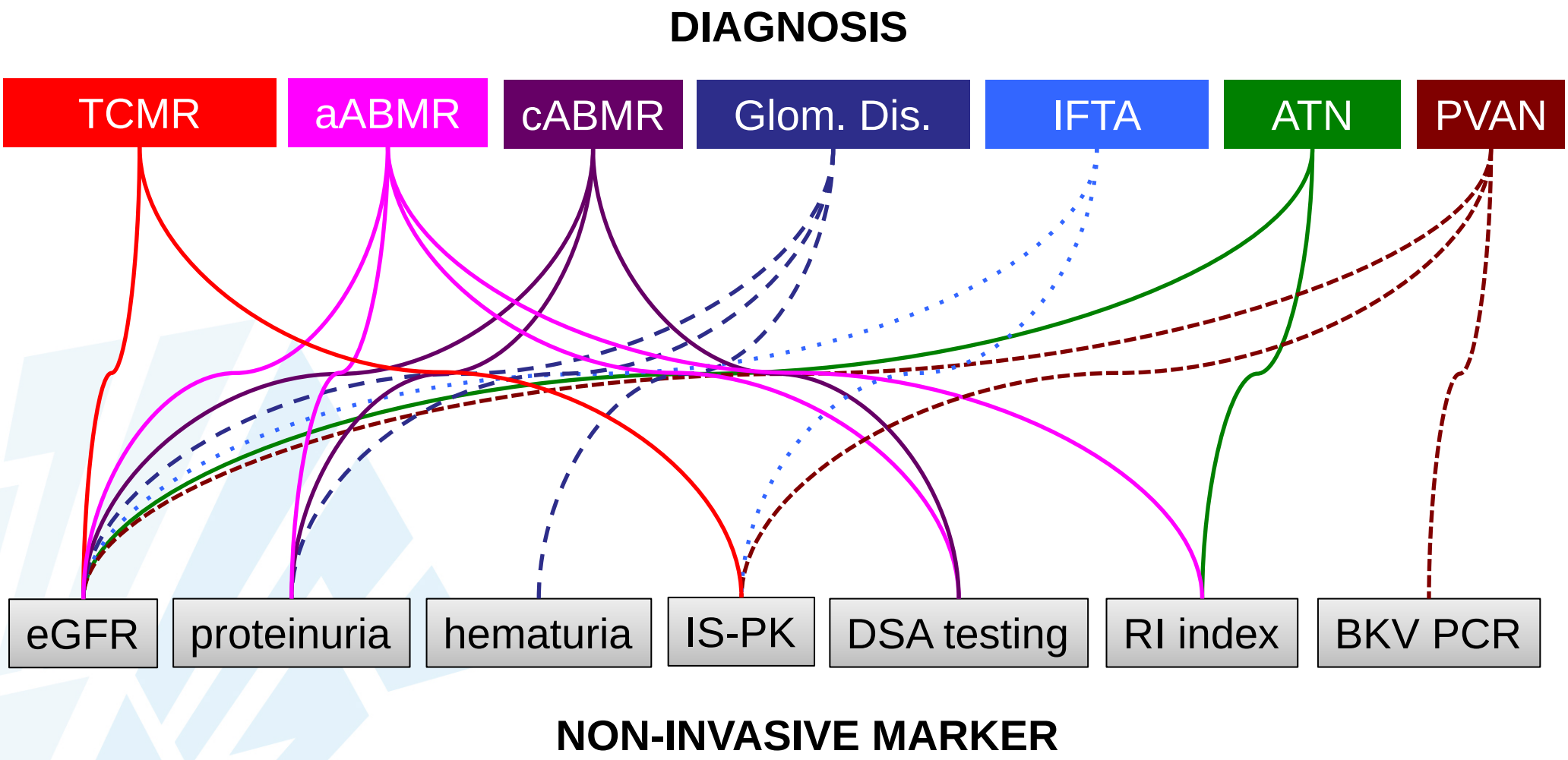
Nankivell BJ, Kuypers DRJ. *Lancet* 2011;378:1428–1437.

Transplantation in 2016



Sellares J et al. Am J Transpl 2012;12:388-399.

Transplantation in 2016



Chen R et al. Cell 2012;148(6):1293-1307.

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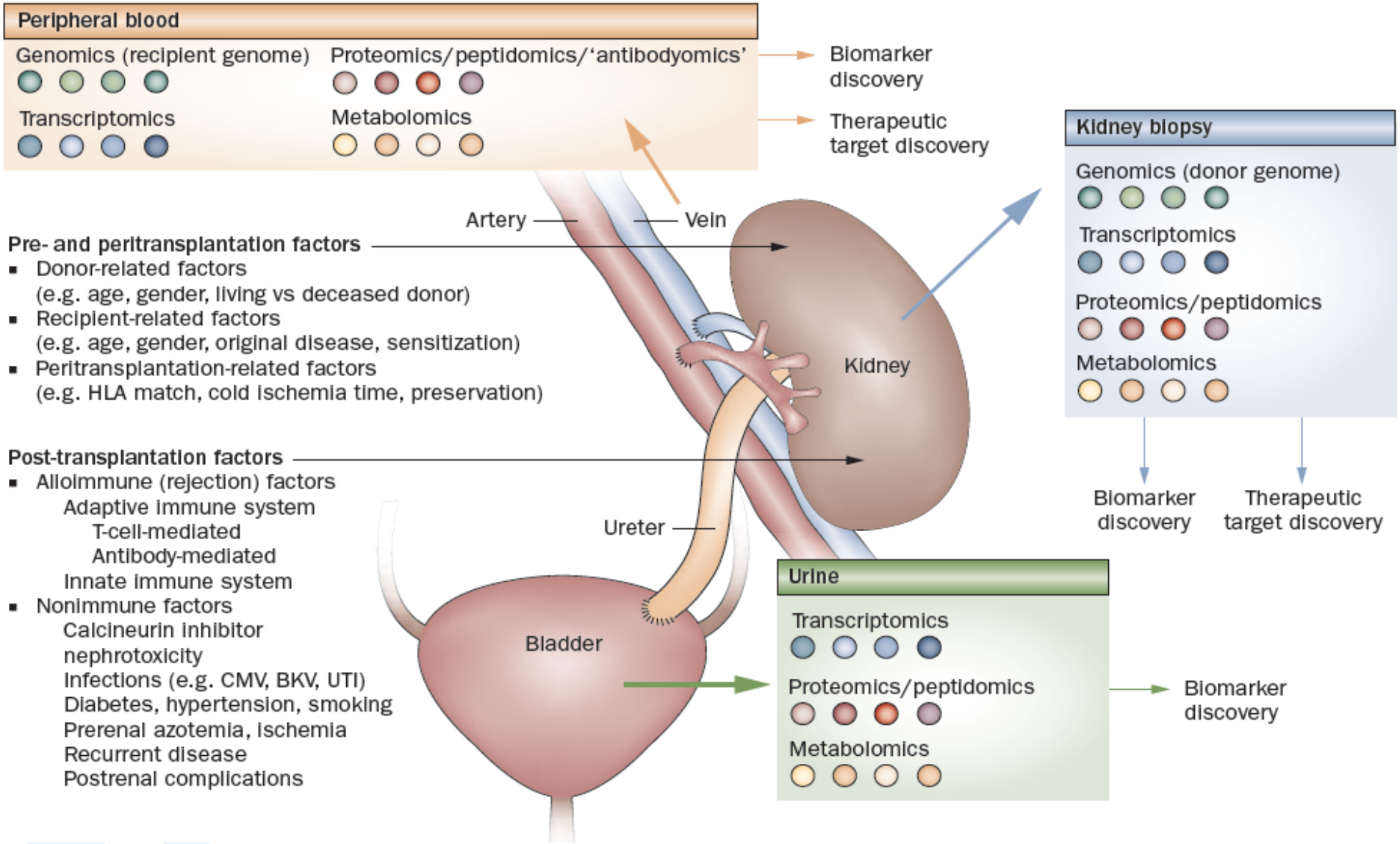
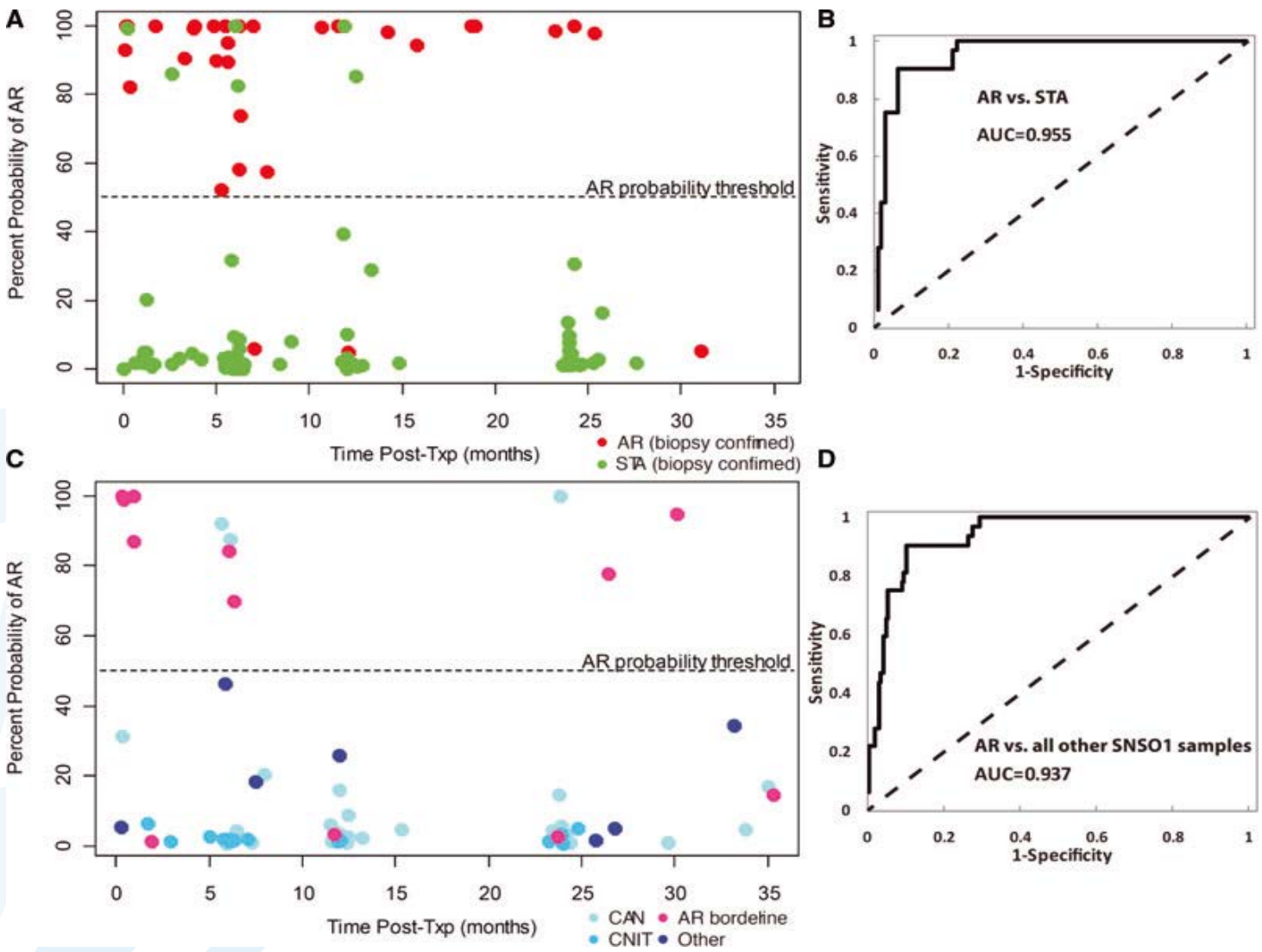
Non-invasive diagnosis – biomarkers



Naesens M et al. Nat Rev Nephrol 2010;6(10):614-628.

Non-invasive diagnosis – biomarkers

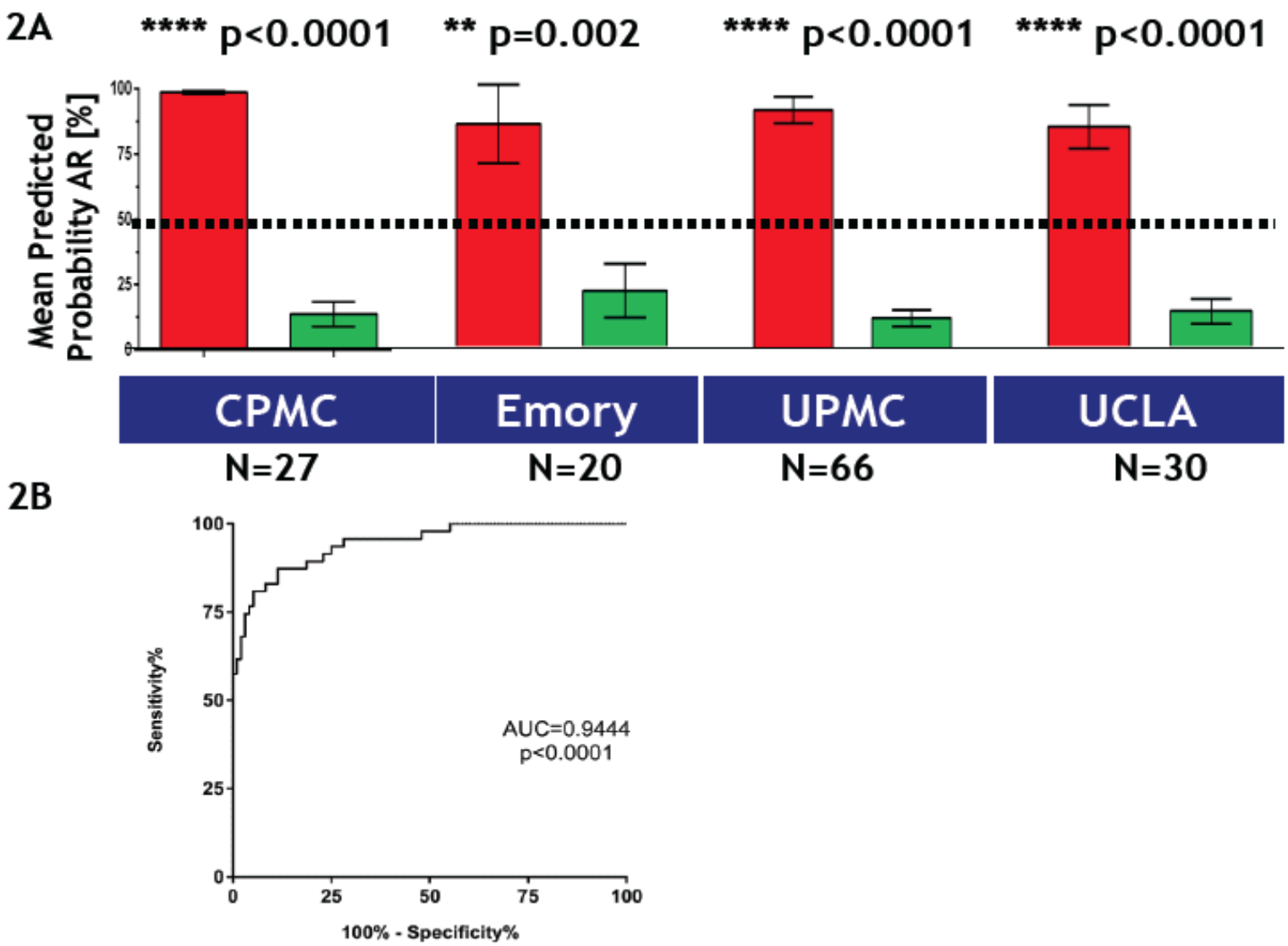


mRNA in blood

5 gene signature
DUSP1, PBEF1, PSEN1, MAPK9 and NKTR

Li L et al. Am J Transplant 2012;12(10):2710-2718.

Non-invasive diagnosis – biomarkers



mRNA in blood

17 gene signature

Roedder S et al. PLoS ONE 2014;11(11):e1001759.

Non-invasive diagnosis – biomarkers

Mariani LH et al. Nephrol Dial Transplant 2015;30:892-898.

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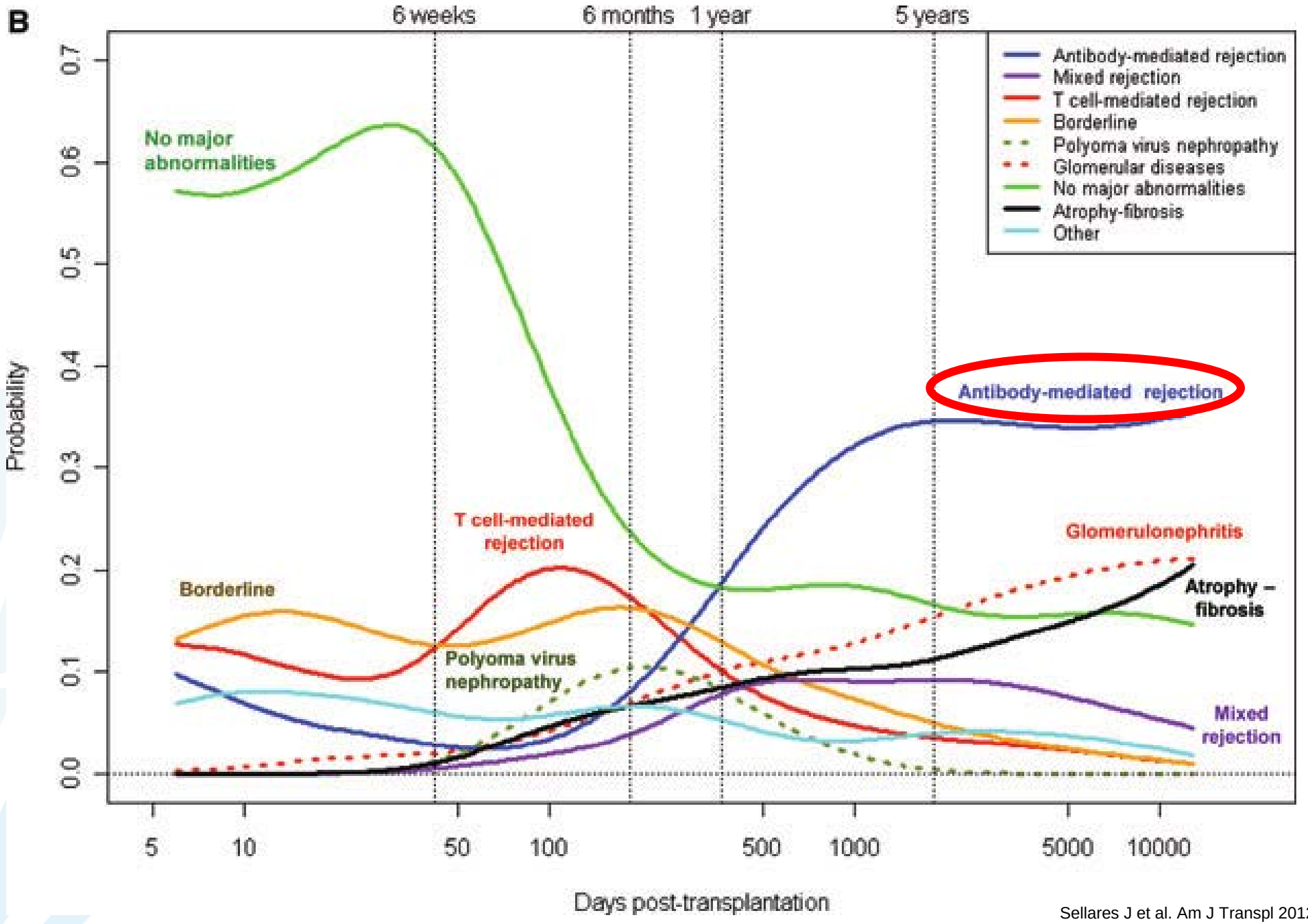
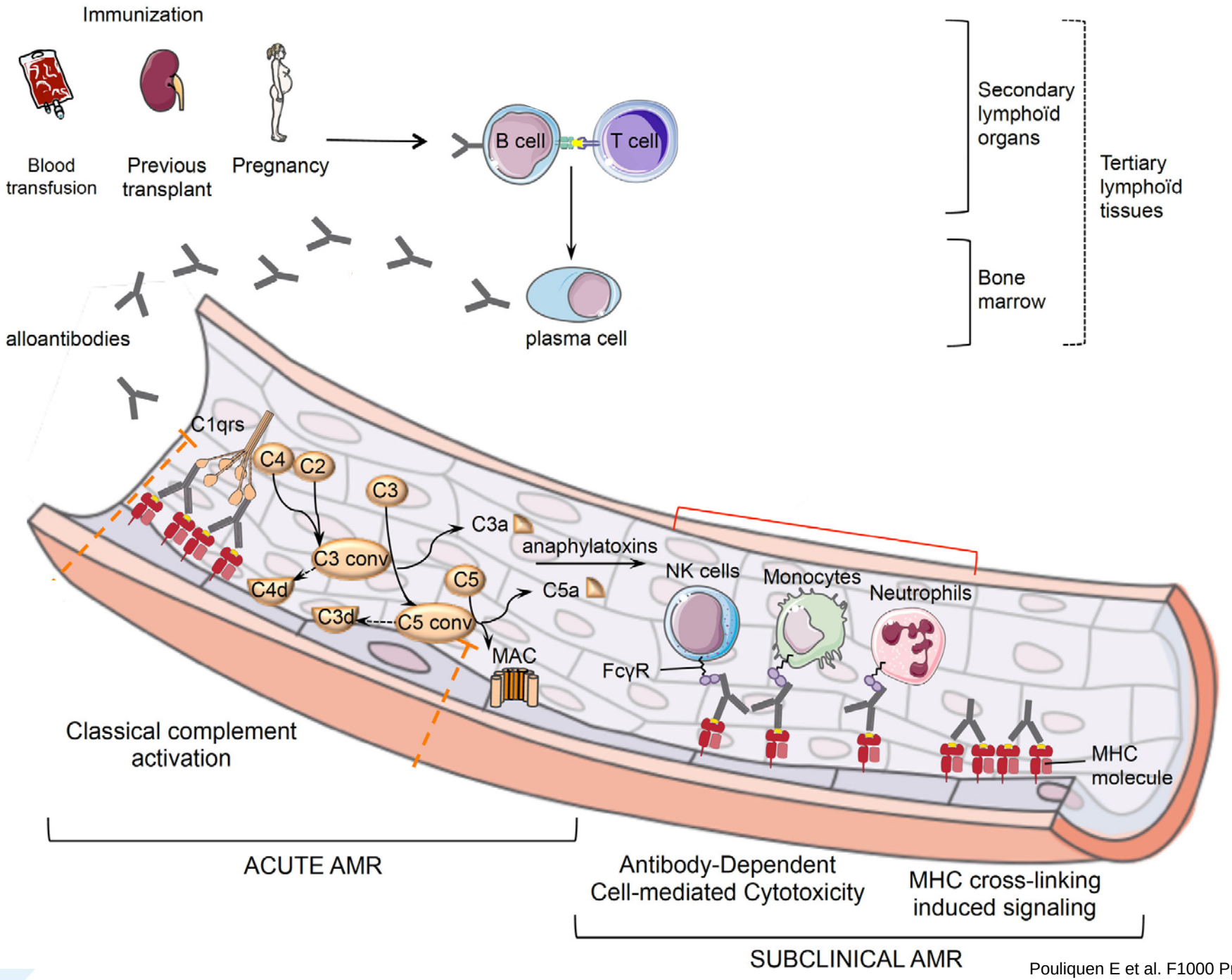
Humoral rejection taking center stage



Sellares J et al. Am J Transpl 2012;12:388-399.

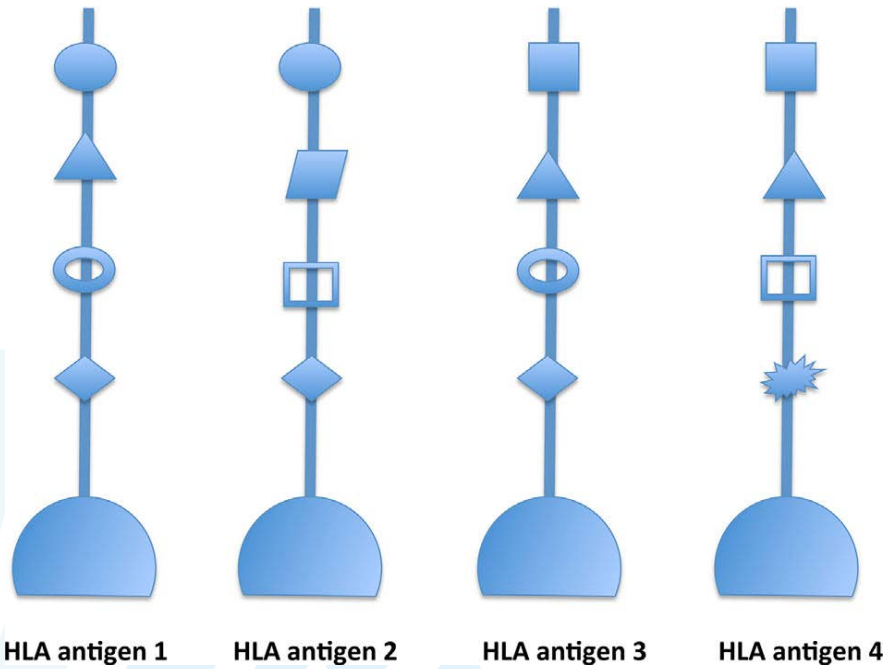
Humoral rejection taking center stage

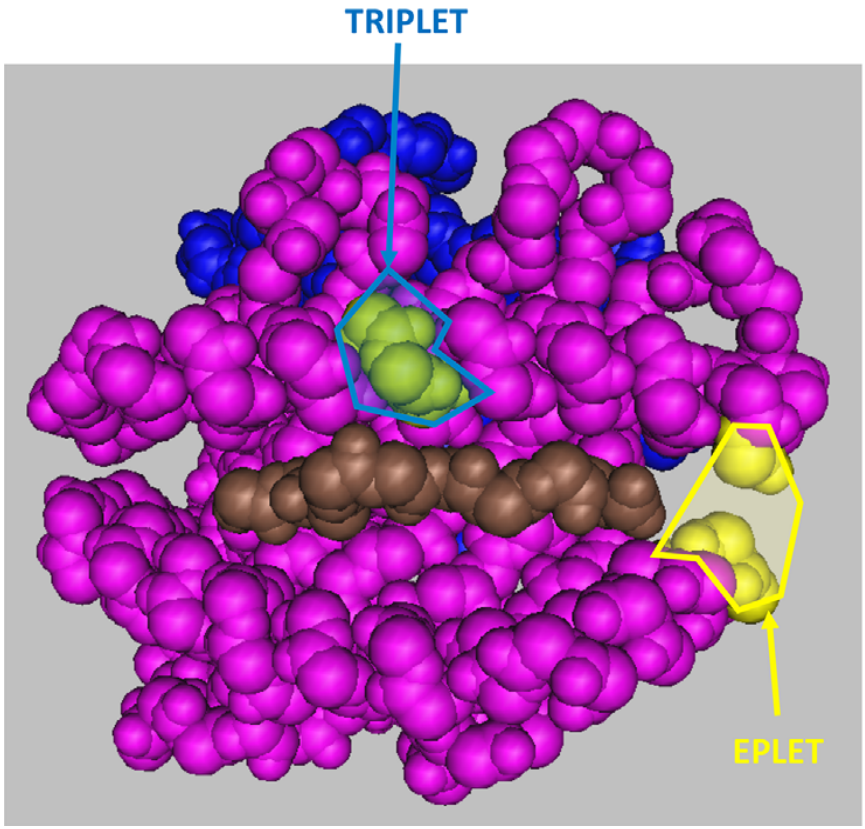


Pouliquen E et al. F1000 Prime Report 2015;7:51.

Humoral rejection taking center stage

From antigen to epitope



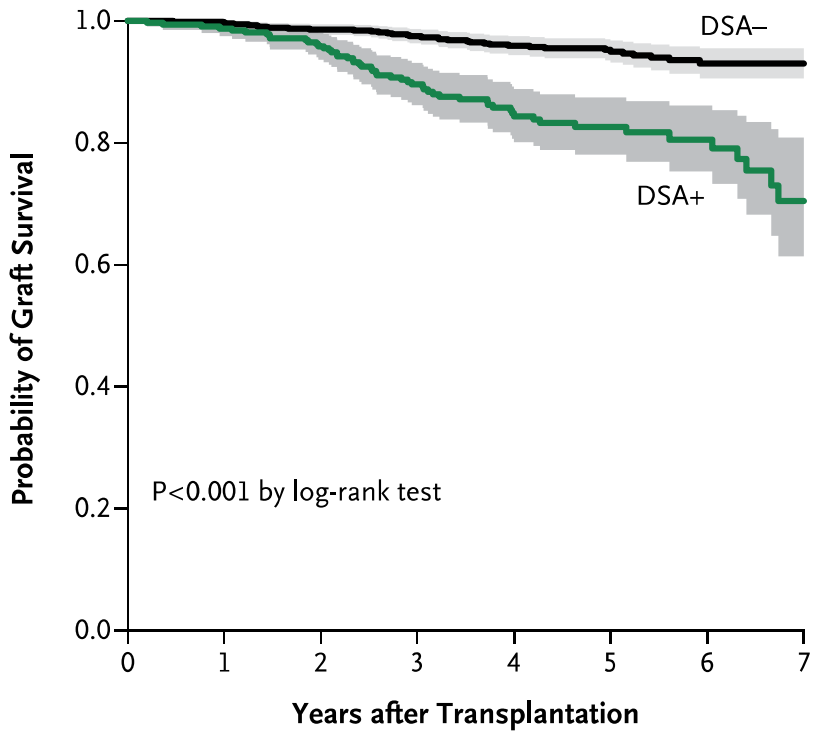


Tambur AR et al. Am J Transpl 2015;15:1148-1154.

Humoral rejection taking center stage

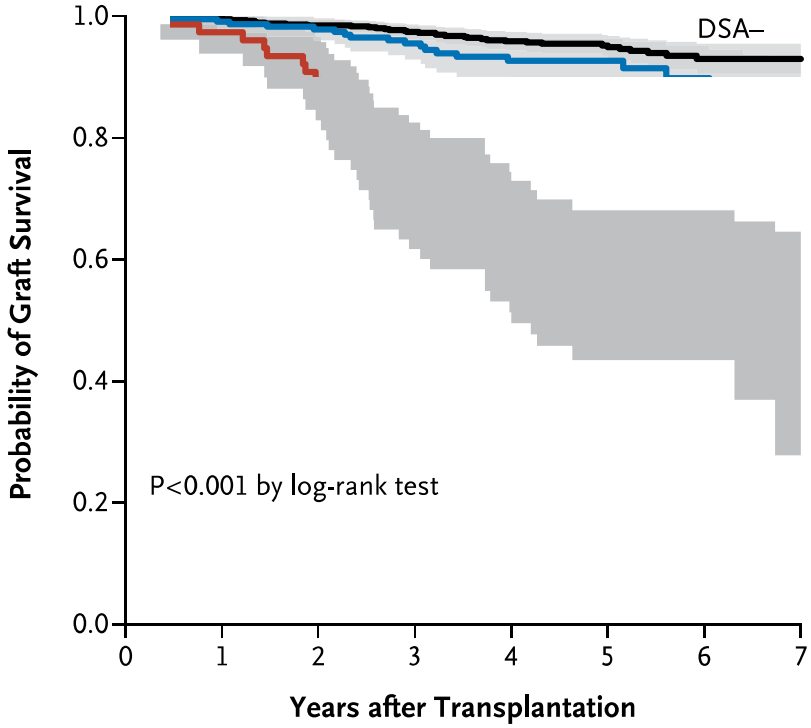
C1q fixing DSA are most detrimental

Kidney-Allograft Survival According to DSA Status



No. at Risk								
DSA–	700	698	667	612	504	338	164	38
DSA+	316	312	295	229	176	100	56	19

Kidney-Allograft Survival According to DSA and C1q Status



No. at Risk								
DSA–	700	698	667	612	504	338	164	38
DSA+, C1q–	239	237	227	181	139	80	44	14
DSA+, C1q+	77	75	68	48	37	20	12	5

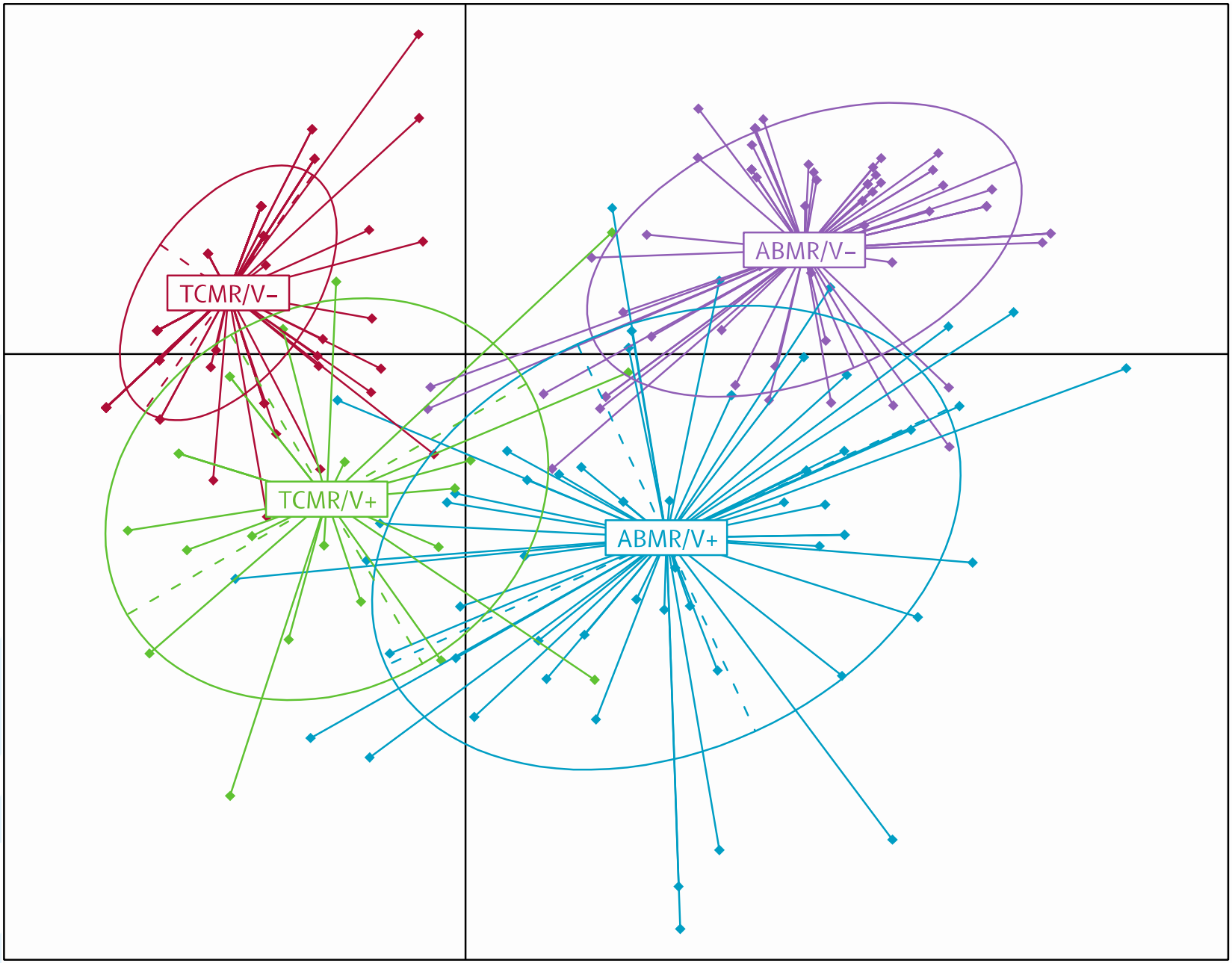
Loupy A et al. N Engl J Med 2013;369:1215-1226.

Humoral rejection taking center stage

But also non-C1q fixing DSA are harmful

Guidicelli C et al. J Am Soc Nephrol 2016;27:615-625.

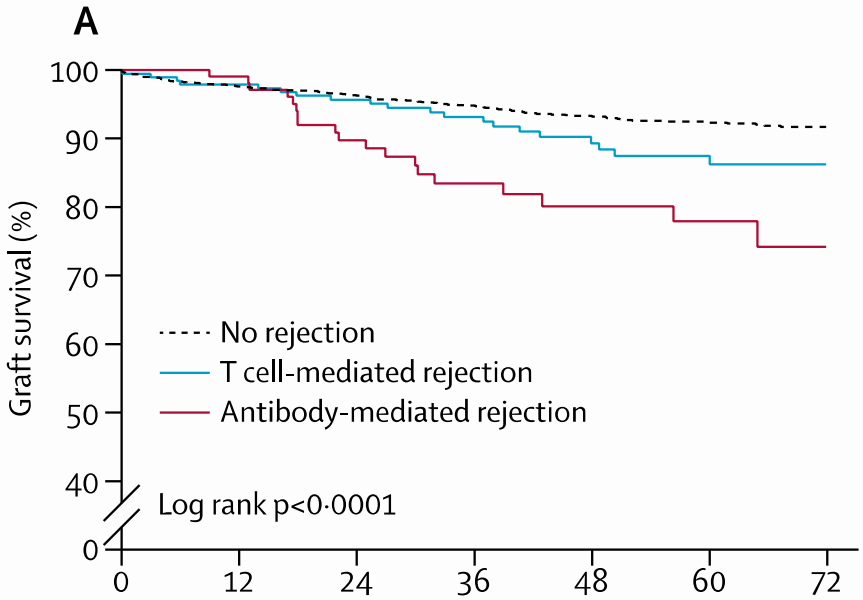
Humoral rejection taking center stage



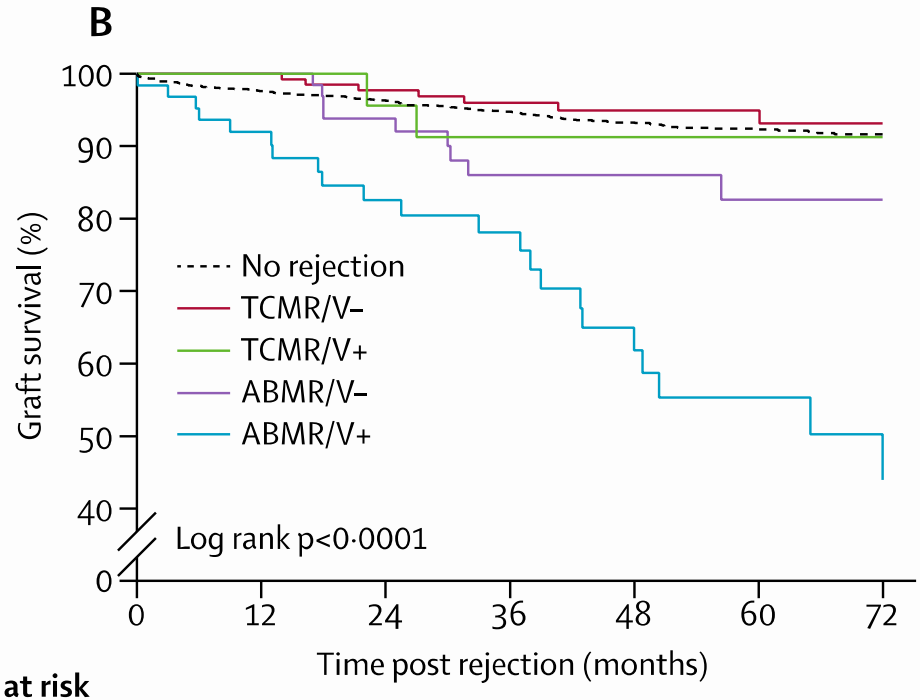
Lefaucheur C et al. Lancet 2013;381:313-319.

Humoral rejection taking center stage

Ab-mediated vascular rejection



Number at risk							
No rejection	1777	1600	1408	1152	933	673	473
T cell-mediated rejection	192	182	163	134	101	71	37
Antibody-mediated rejection	110	100	78	61	40	26	12

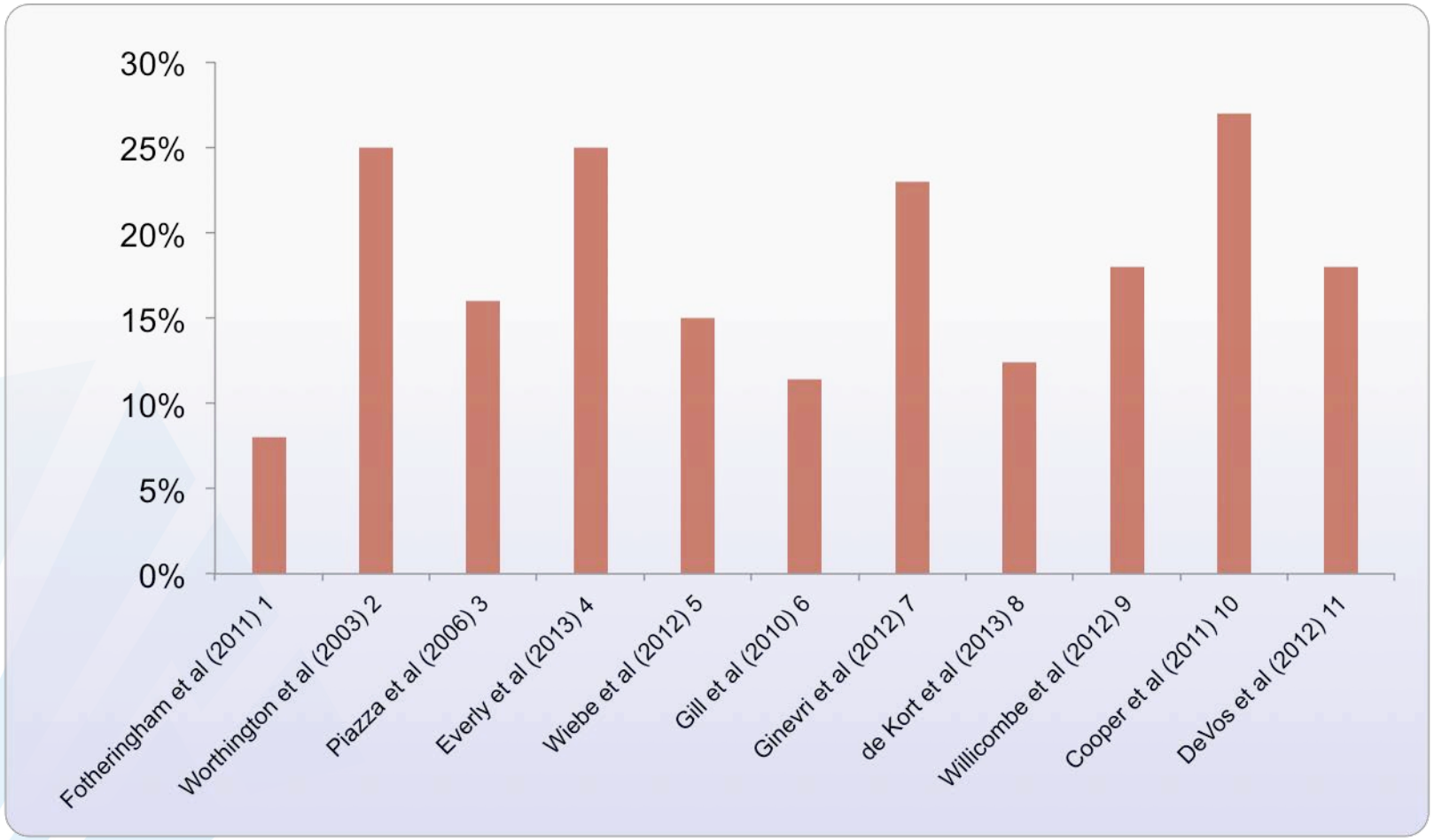


Number at risk							
No rejection	1777	1600	1408	1152	933	673	473
TCMR/V–	139	136	121	101	77	54	29
TCMR/V+	26	26	23	20	15	12	4
ABMR/V–	73	68	56	42	28	19	7
ABMR/V+	64	52	41	32	21	12	9

Lefaucheur C et al. Lancet 2013;381:313-319.

Humoral rejection taking center stage

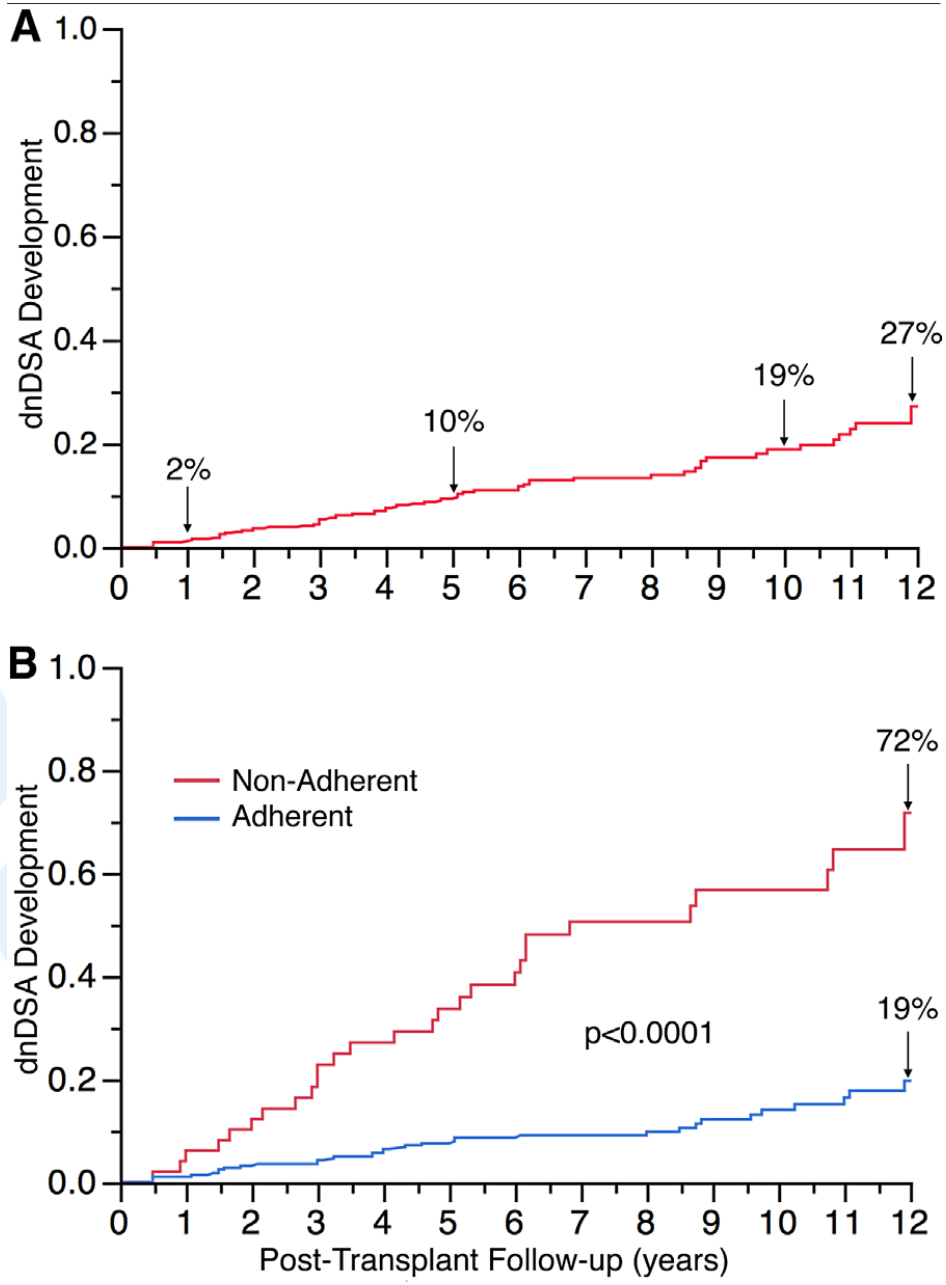
dnDSA CUMULATIVE PREVALENCE IN KIDNEY TRANSPLANTATION DOCUMENTED IN THE LITERATURE



1. Fotheringham J et al. *Transplantation* 2011;91:991–996.
2. Worthington JE et al. *Transplantation* 2003;75:1034–1040.
3. Piazza A et al. *Clin Transplant* 2006;323–336.
4. Everly MJ et al. *Transplantation* 2013;95:410–417.
5. Wiebe C et al. *Am J Transplant* 2012;12:1157–1167.
6. Gill JS et al. *Transplantation* 2010;89:178–184.
7. Ginevri F et al. *Am J Transplant* 2012;12:3355–3362.
8. de Kort H et al. *Am J Transplant* 2013;13:485–492.
9. Willicombe M et al. *Transplantation* 2012;94:172–177.
10. Cooper JE et al.*Transplantation* 2011;91:1103–1109.
11. DeVos JM et al. *Kidney Int* 2012;82:598–604.

Humoral rejection taking center stage

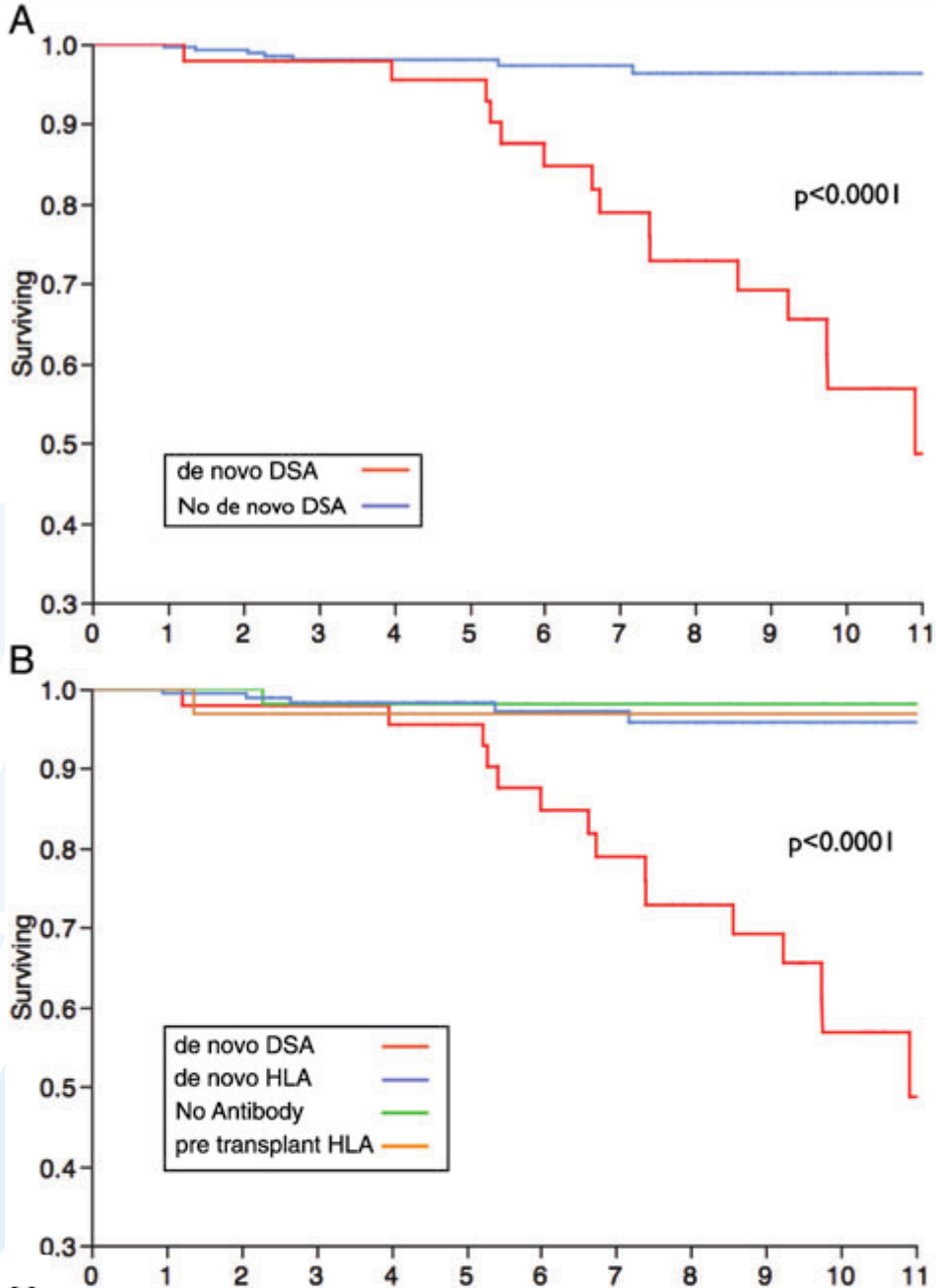
dnDSAs accumulate over time – non-adherence increases the risk of dnDSA developing



Wiebe C et al. Am J Transpl 2015;15:2921-2930.

Humoral rejection taking center stage

dnDSAs are associated with decreased allograft survival



Prospective study: 315 consecutive kidney transplant recipients

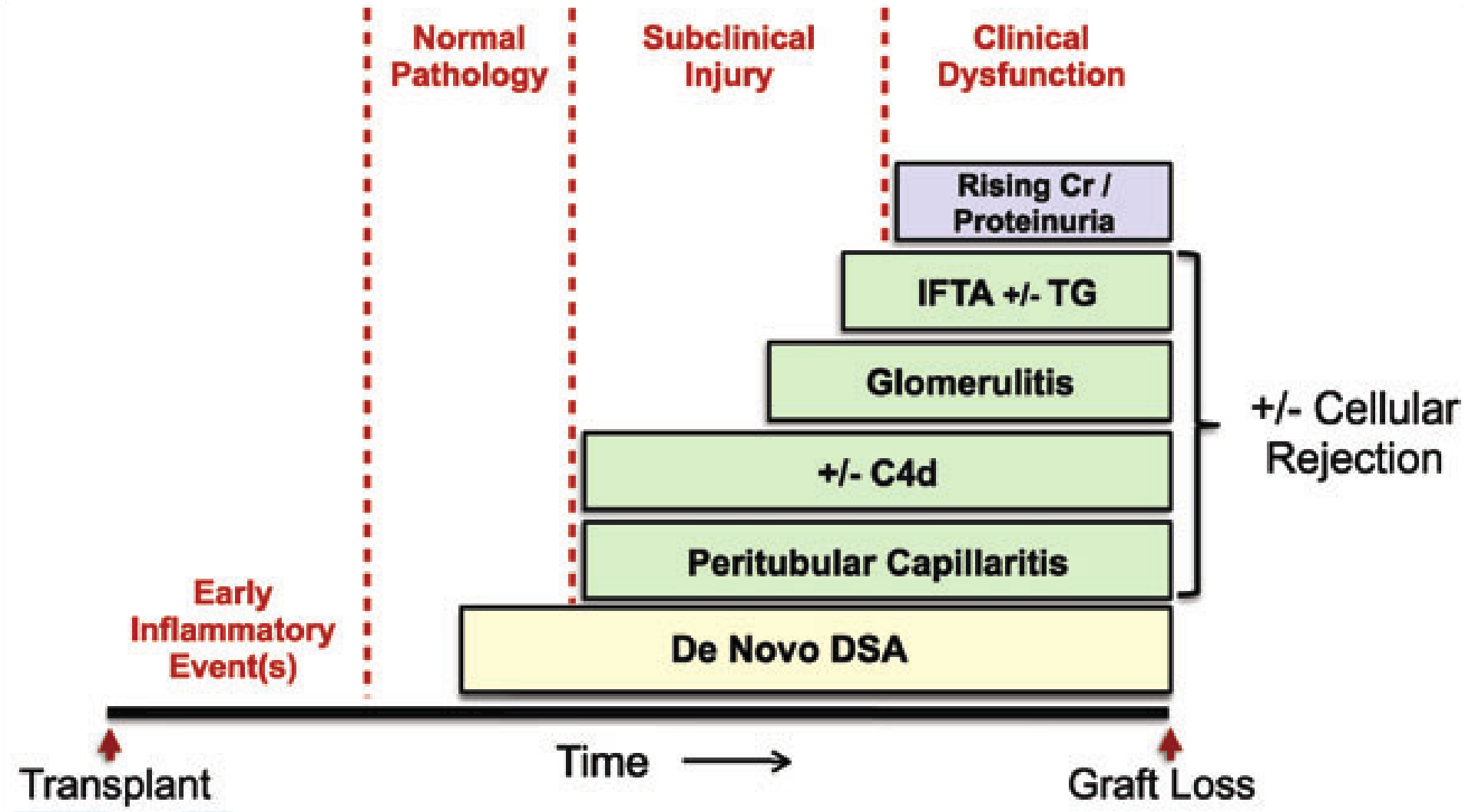
Non-adherence is a predictor of de novo DSA (OR 8.75; p<0.001)

Non-adherent recipients: 49% dnDSA versus 8% in adherent patients (p<0.001)

De novo DSA are associated with a significant reduction in 10-year graft survival

Wiebe C et al. Am J Transpl 2012;12:1157-1167.

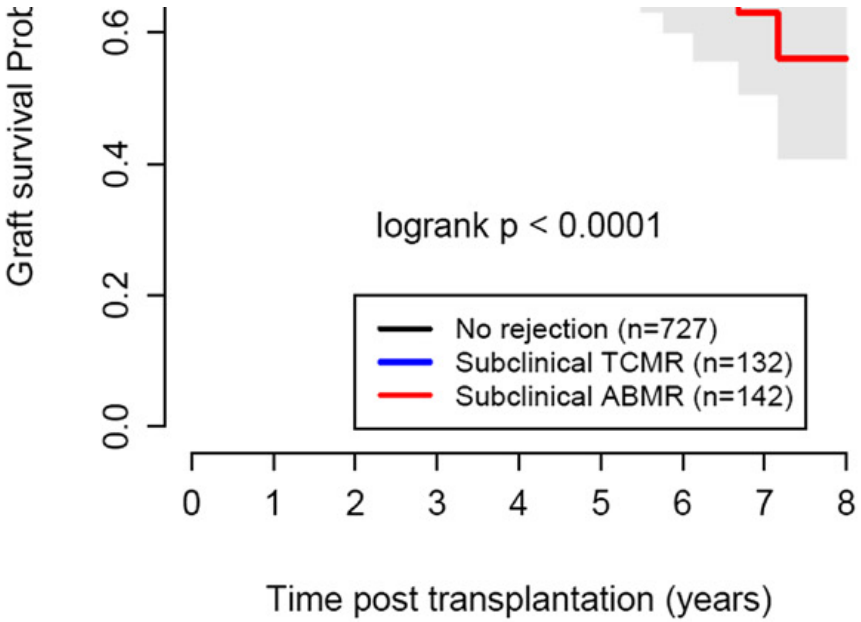
Humoral rejection taking center stage



Wiebe C et al. Am J Transpl 2012;12:1157-1167.

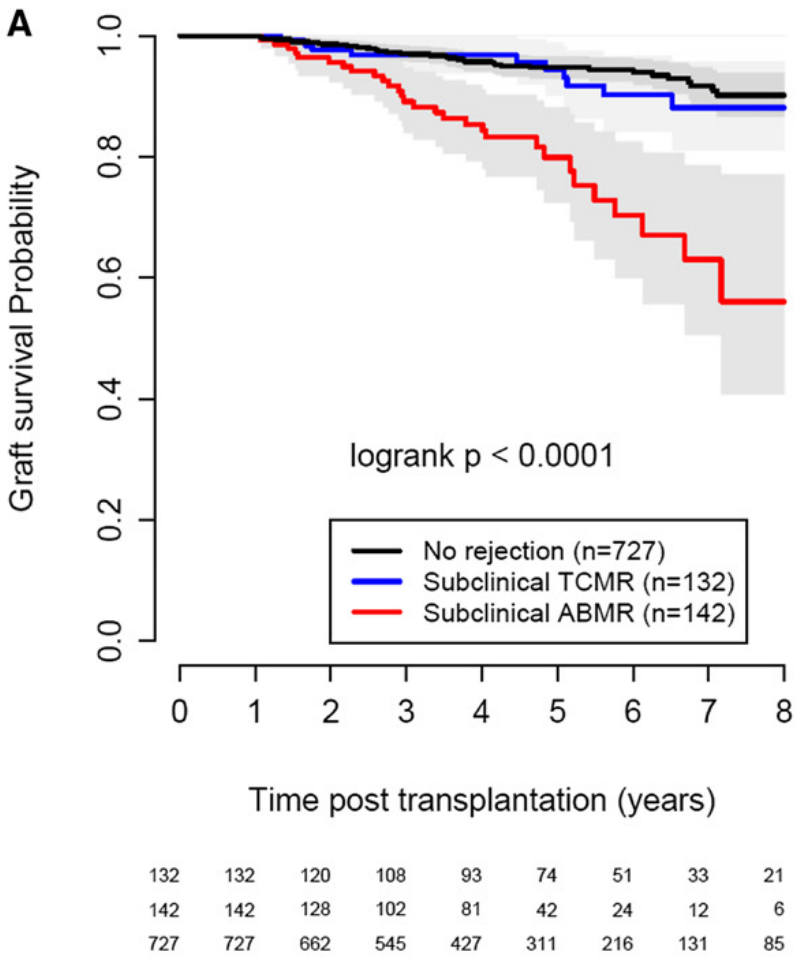
Humoral rejection taking center stage

Subclinical ABMR is associated with worse allograft survival



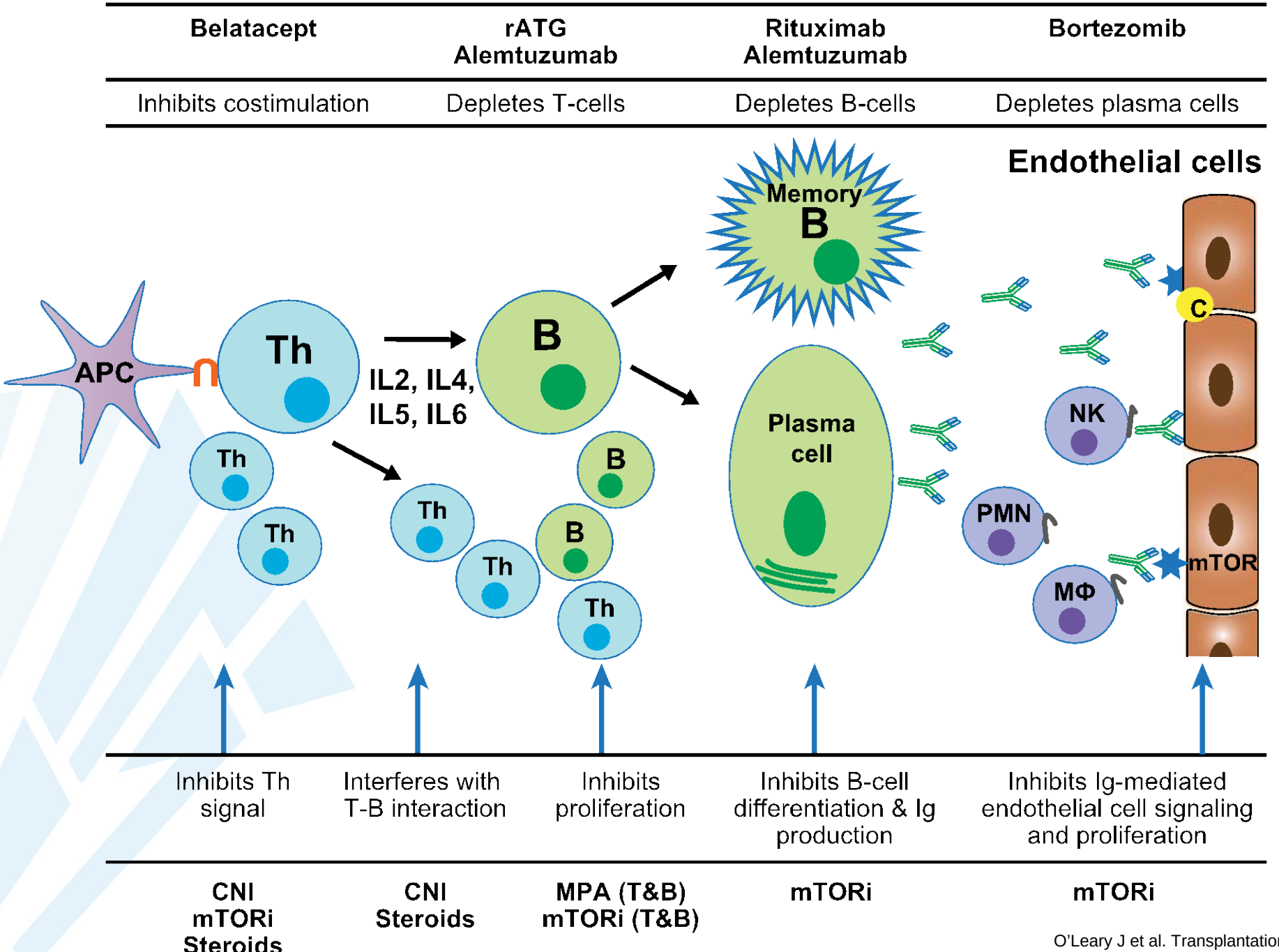
Subclinical TCMR
Subclinical ABMR
No rejection

No ABMR
ABMR



Loupy A et al. Am J Transpl 2015;26:1721-1731.

Humoral rejection taking center stage



O'Leary J et al. Transplantation 2016;100:39-53.

Humoral rejection taking center stage

Tacrolimus cessation: not a good idea

4 screen failures
1 withdrew

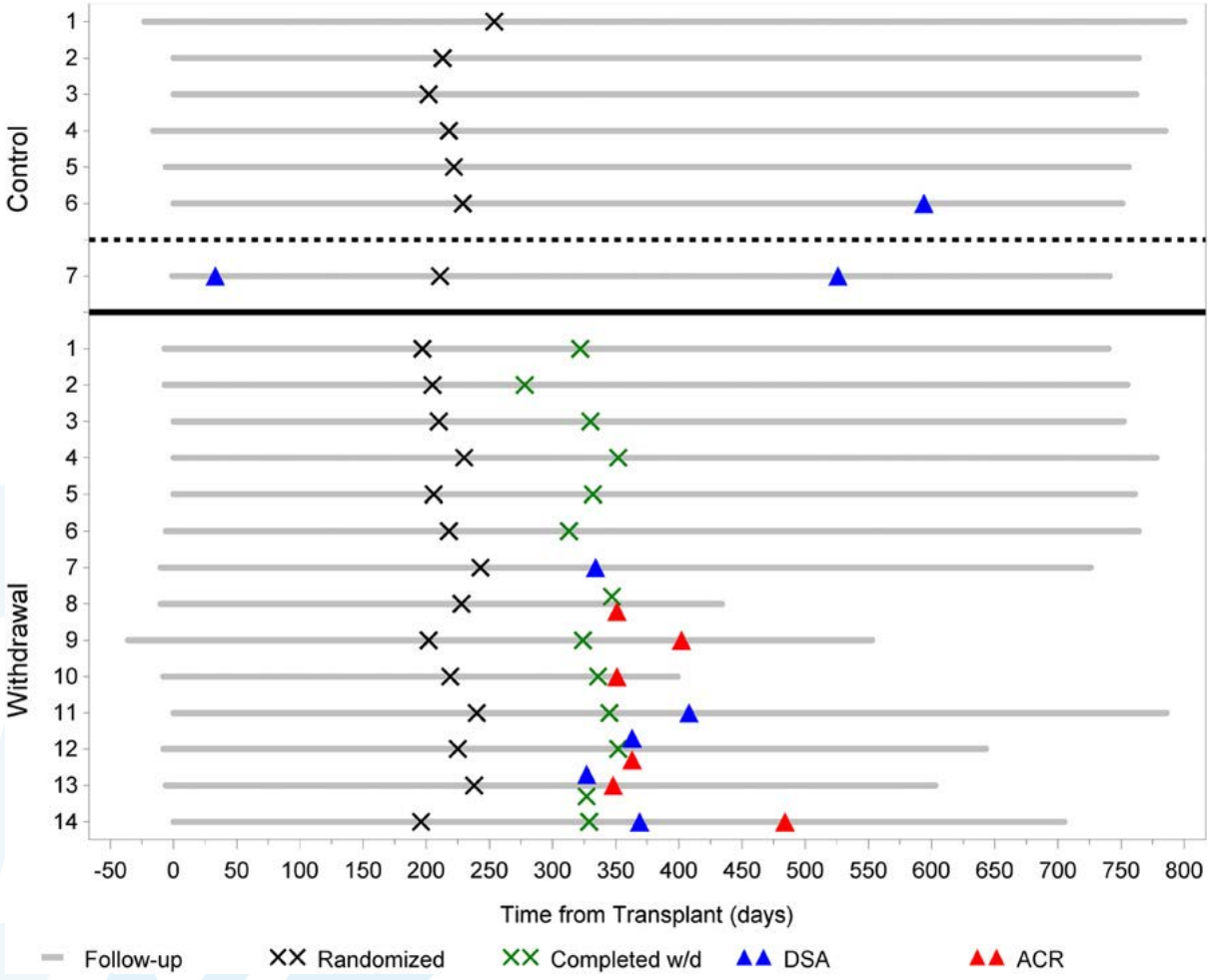
26 Transplanted, not randomized subjects

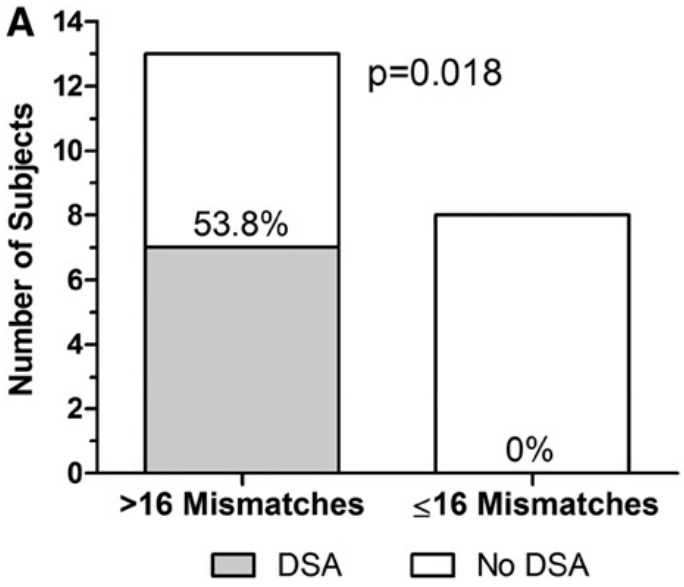
- 8 Withdrawal of Consent
- 1 Lost to Follow-up
- 14 Ineligible for randomization
- 3 Post-transplant follow-up when study stopped

Hricik DE et al. J Am Soc Nephrol 2015;26:3114-3122.

Humoral rejection taking center stage

Tacrolimus cessation: not a good idea

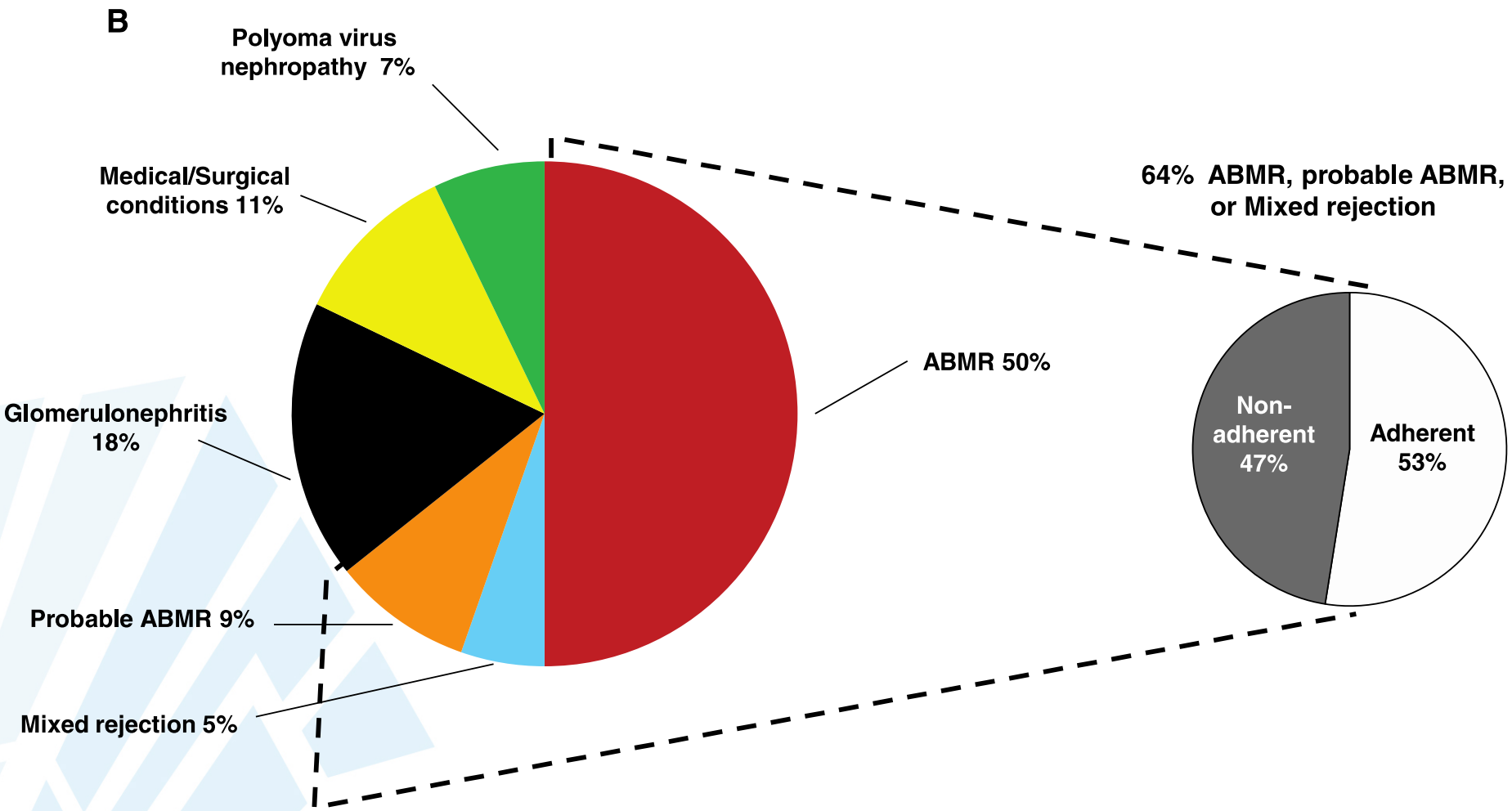




Hricik DE et al. J Am Soc Nephrol 2015;26:3114-3122.

Humoral rejection taking center stage

ABMR and non-adherence



Sellares J et al. Am J Transpl 2012;12:388-399.

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Don’t loose sight of the basics: non-adherence

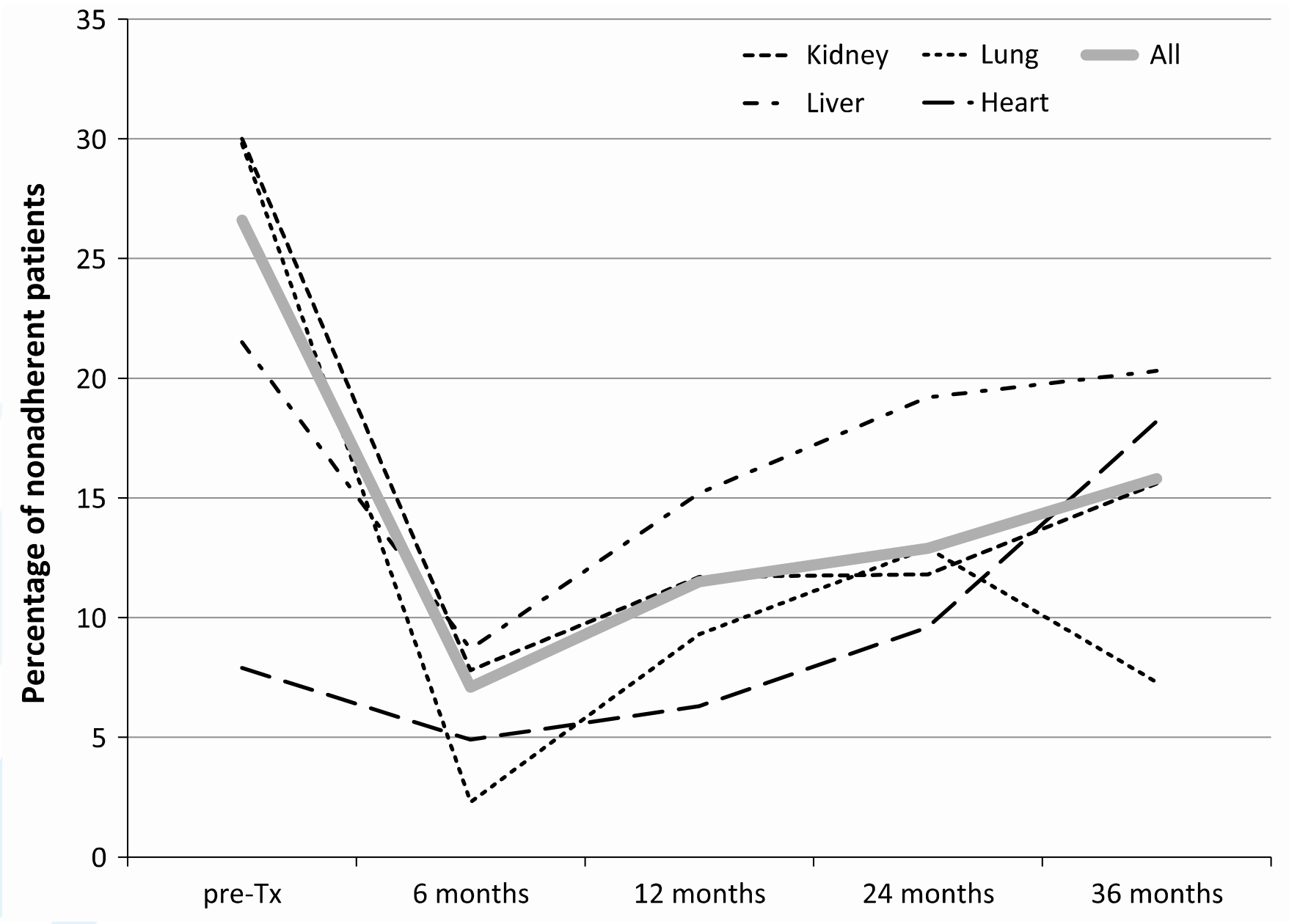
Non-adherence

- Often undetected and unintentional
  - At any point after transplantation
  - Undetectable drug levels
  - Not taking:
  - Medicine – missing the occasional dose
  - Right dose of medication
  - Medicine at the right time
  - Medicine appropriately (eg with or without food)

- Non-adherence encompasses more than just the patients who are deliberately non-adherent
  - Unintentional non-adherence is a passive process, whereas intentional non-adherence is an active process[2]
  - Patients unintentionally fail to adhere to medication through forgetfulness, carelessness, circumstances outside their control[2]

Sellares J et al. *Am J Transplant* 2012;12:388–399.
Gadkari AS, McHorney CA. *BMC Health Serv Res* 2012;12.

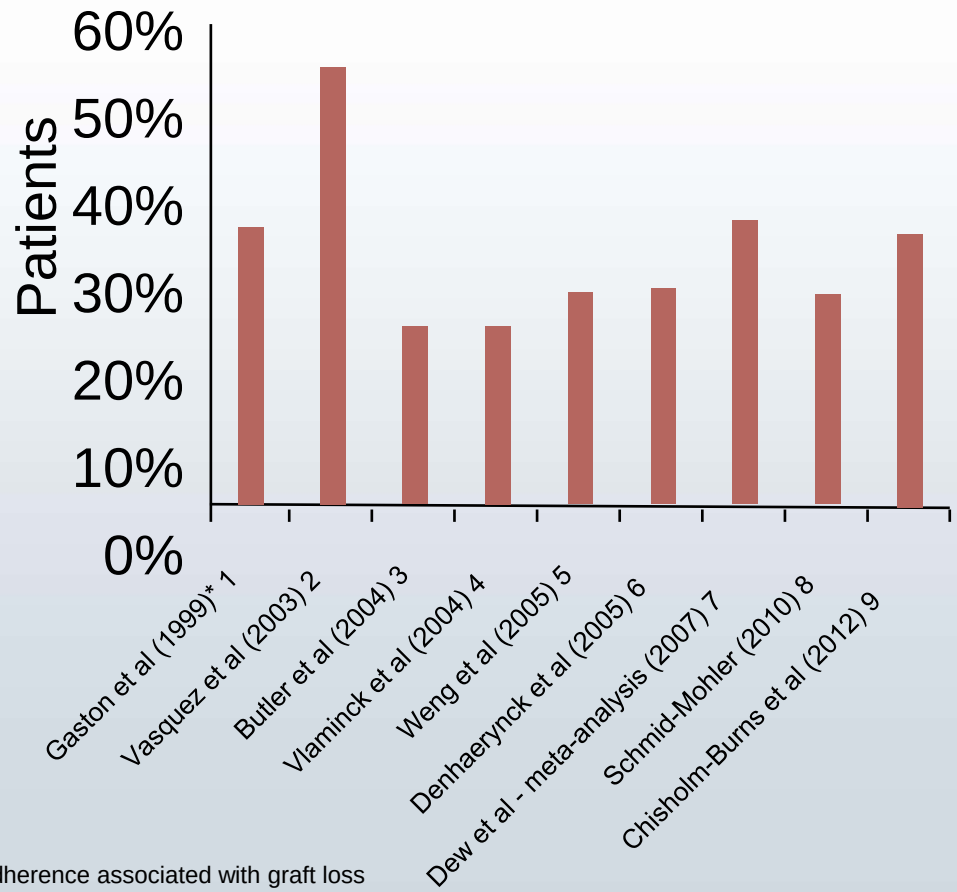
Don’t loose sight of the basics: non-adherence

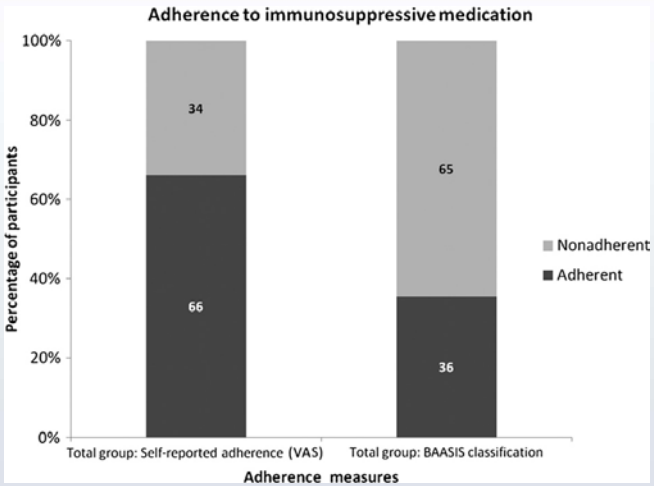


De Geest S et al. Transpl Int 2014;27:657-666.

Don’t loose sight of the basics: non-adherence

NON-ADHERENCE RATES IN KIDNEY TRANSPLANTATION





* Included only non-adherence associated with graft loss

1. Gaston RS et al. *Transplant Proc* 1999;31(suppl 4A):21S−23S.
2. Vasquez EM et al. *Am J Health Syst Pharm* 2003;60:266−269.
3. Butler JA et al. *Transplantation* 2004;77:769−776.
4. Vlaminck H et al. *Am J Transplant* 2004;4:1509−1517.
5. Weng FL et al. *J Am Soc Nephrol* 2005;16:1839−1848.
6. Denhaerynck K et al. *Transpl Int* 2005;18:1121−1139.
7. Dew MA et al. *Transplantation* 2007;83:858−873.
8. Schmid-Mohler et al. *Clin Transplant* 2010;24:213−222.
9. Chisholm-Burns M et al. *Clin Transplant* 2012;26:706−713.
10. Massey EK et al. *Transplantation* 2015;99:e89-e96

Don’t loose sight of the basics: non-adherence

Non-adherence

- Has a significant impact on graft survival (OR of graft failure 7x)

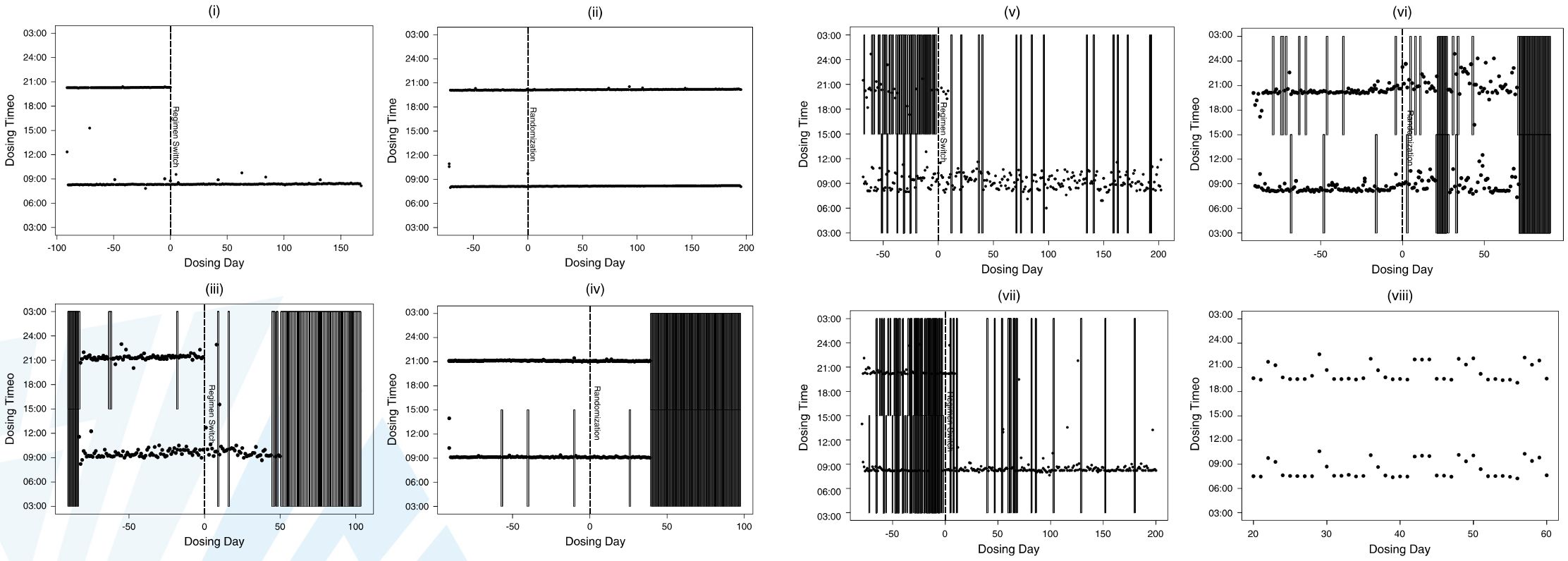
Study	Graft loss associated with non-adherence
Butler et al. 2004[1]	36% (14–65)
Brown et al. 2009[2]	26%
Denhaerynck et al. 2005[3]	16%
Guerra et al. 2012[4]	45%
Prendergast et al. 2010[5]	36%

- Concerns about non-adherence were recorded 10x more frequently in patients whose graft failed (32%) vs those whose graft survived (3%)

1. Butler JA et al. *Transplantation* 2004;77:769−777.
2. Brown KL et al. *Clin Transplant* 2009;23:454–461.
3. Denhaerynck K et al. *Transpl Int* 2005;18:1121–1133.
4. Guerra G et al. *J Am Soc Nephrol* 2012;22:1758–1768.
5. Prendergast MB et al. *Clin J Am Soc Nephrol* 2010;5:1305–1311.
6. Sellares J et al. *Am J Transplant* 2012;12:388–399.

Don’t loose sight of the basics: non-adherence

Once-daily and twice-daily dosing affects adherence



Kuypers DRJ et al. Transplantation 2013;95:333-340.

Don’t loose sight of the basics: non-adherence

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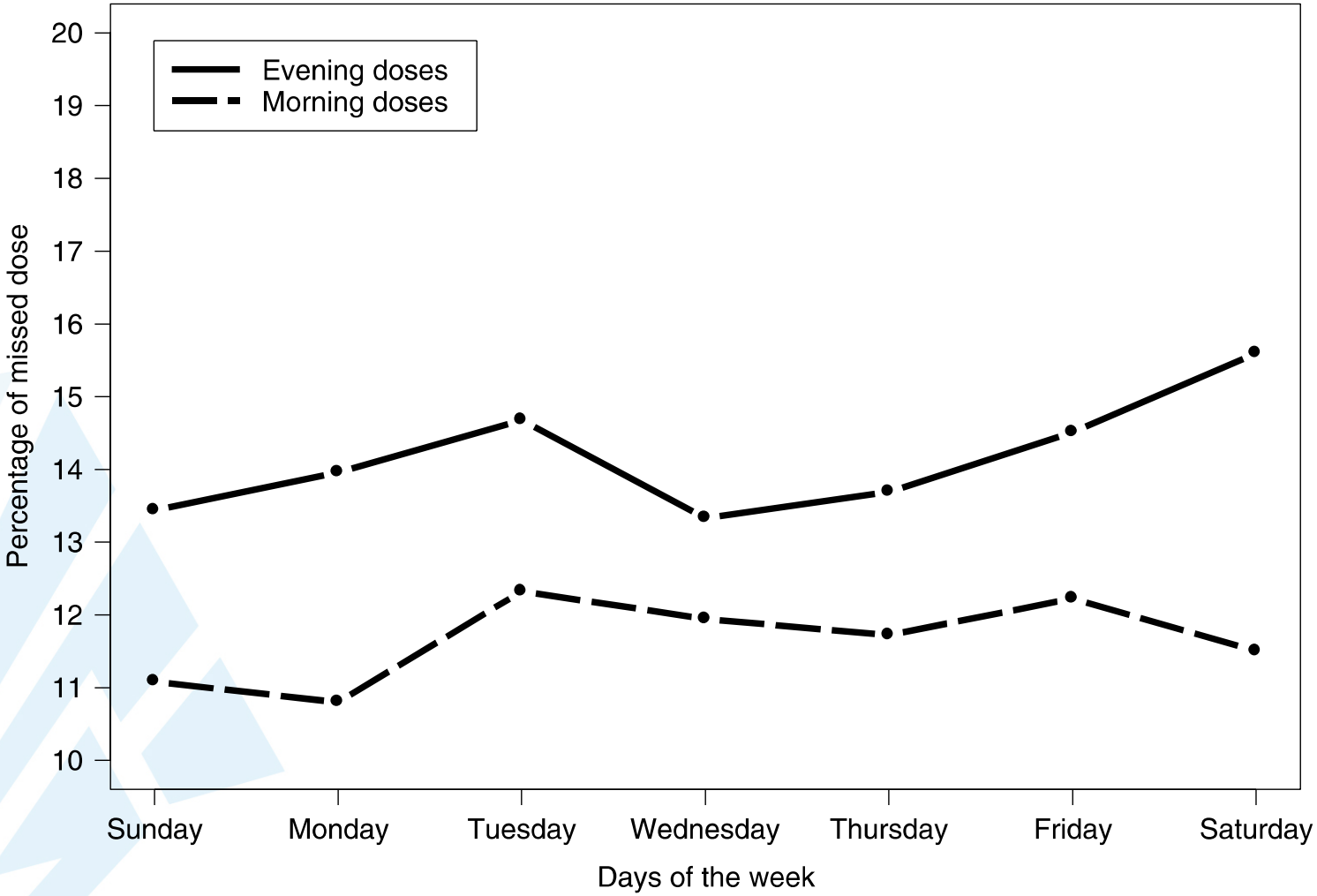
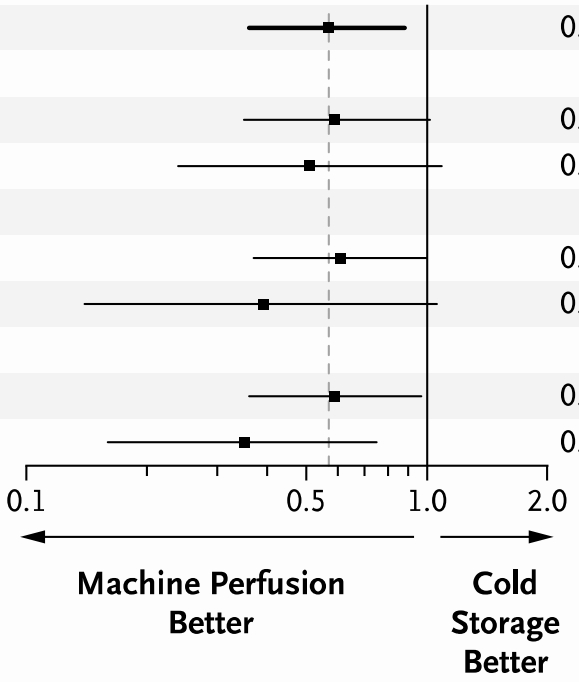


Kuypers DRJ et al. Transplantation 2013;95:333-340.

Don’t loose sight of the basics: machine hypothermic perfusion

Risk for delayed-graft function

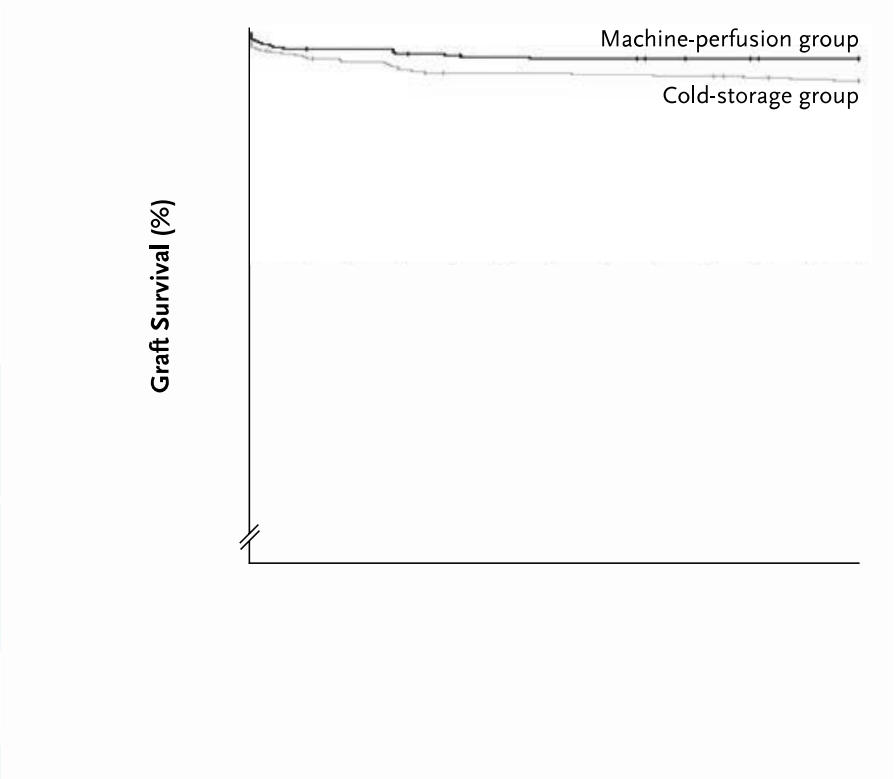
Subgroup	No. of Patients (%)	Machine-Perfusion Group	Cold-Storage Group	Adjusted Odds Ratio (95% CI)	P Value
		no. of events (%)			
Overall	672 (100)	70 (21)	89 (27)	0.57 (0.36–0.88)	
Donor criteria					0.75
Standard-criteria donation	484 (72)	48 (20)	60 (25)	0.59 (0.35–1.02)	
Expanded-criteria donation	188 (28)	22 (23)	29 (31)	0.51 (0.24–1.09)	
Donation procedure (main data set)					0.42
Donation after brain death	588 (88)	48 (16)	61 (21)	0.61 (0.37–1.00)	
Donation after cardiocirculatory death	84 (13)	22 (52)	28 (67)	0.39 (0.14–1.06)	
Donation procedure (extended data set)					0.26
Donation after brain death	588 (78)	48 (16)	61 (21)	0.59 (0.36–0.97)	
Donation after cardiocirculatory death	164 (22)	44 (54)	57 (70)	0.35 (0.16–0.75)	

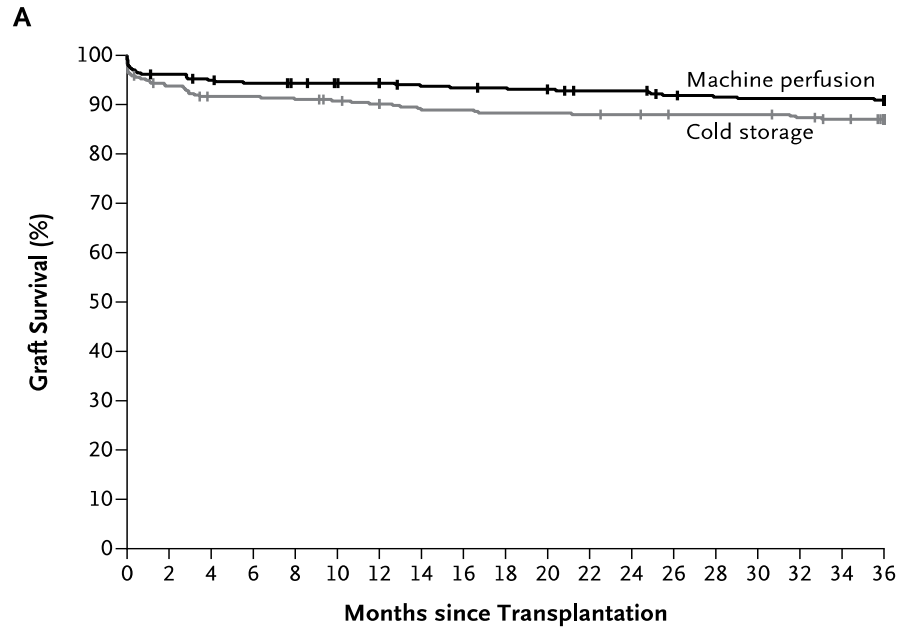


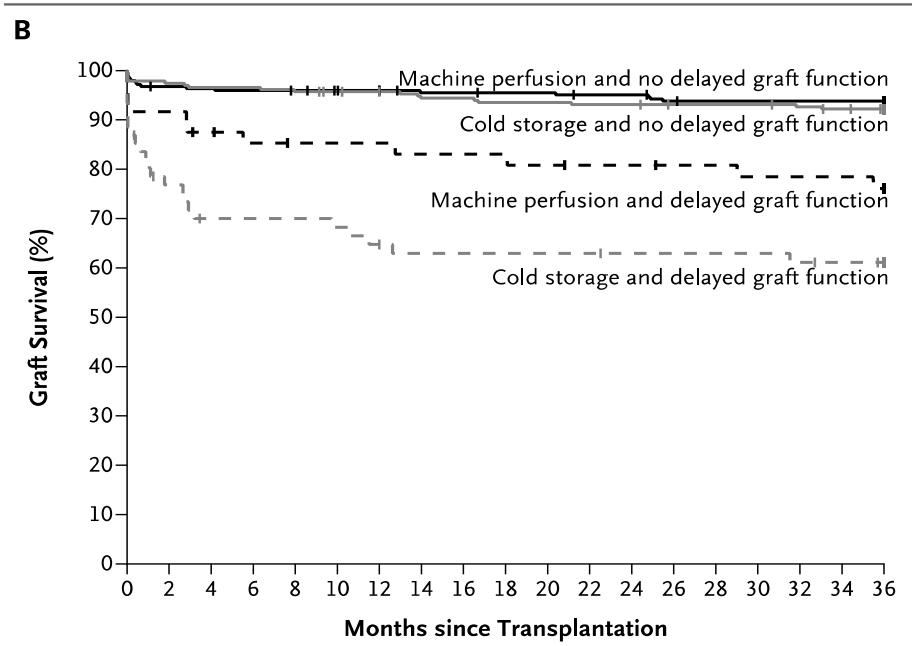
Moers C et al. N Engl J Med 2009;360:7-19.

Don’t loose sight of the basics: machine hypothermic perfusion

Improved survival – particularly in DBD kidney transplants







Moers C et al. N Engl J Med 2009;360:7-19.
Moers C et al. N Engl J Med 2012;366:770-771.

Don't loose sight of the basics: machine hypothermic perfusion

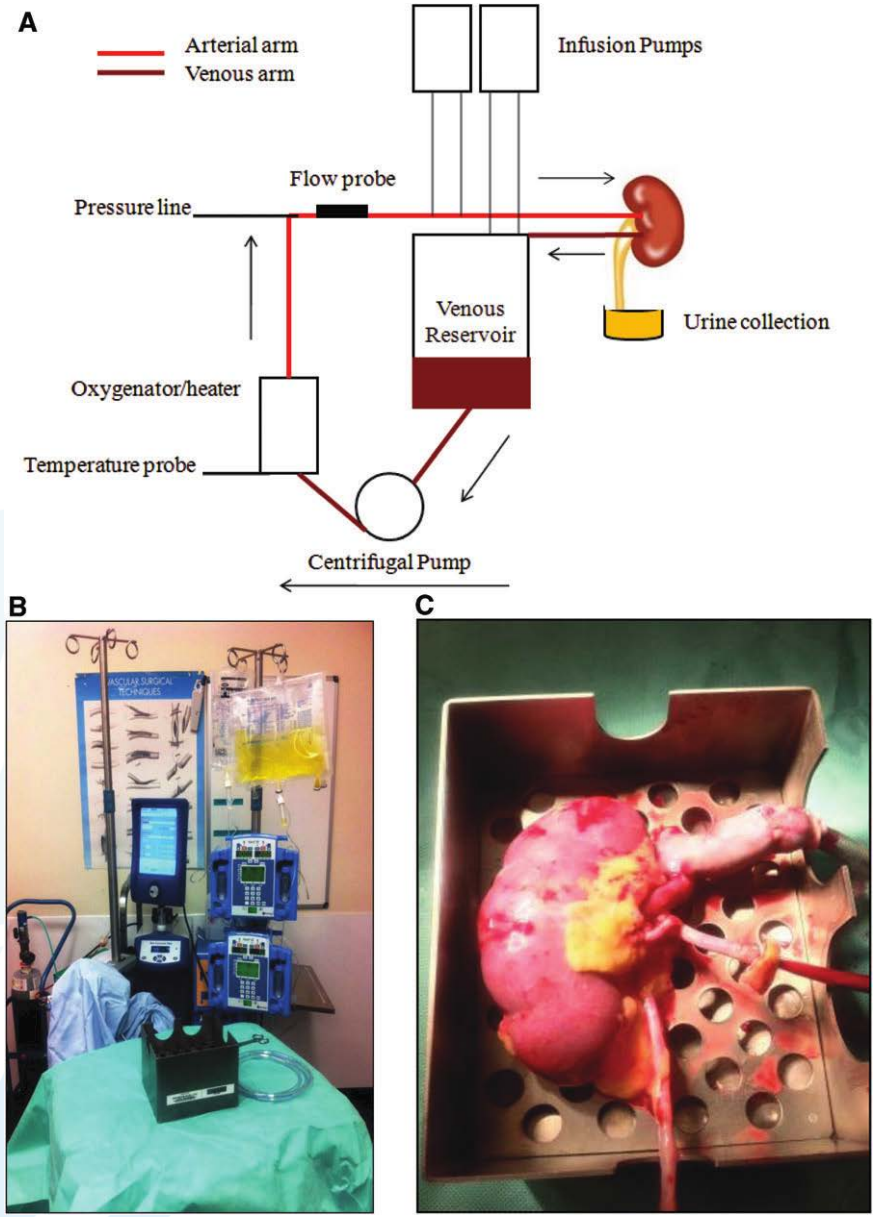
Decreased DGF but no improved allograft survival in DCD kidney transplants

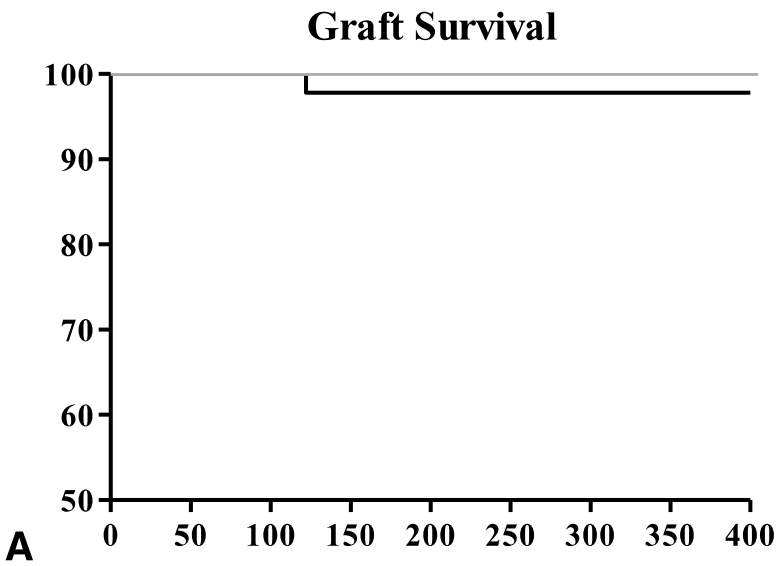
Variable	Machine Perfusion Group (N = 82)	Static Cold Storage Group (N = 82)	*P*
*Delayed graft function**			
Incidence, n (%)	44 (53.7)	57 (69.5)	0.007
Duration			0.021
<7 d	12	6	
≥7 d	32	51	
Median duration, d	9 (1–48)	13 (2–43)	0.082
Functional delayed graft function,† n (%)	16 (19.5)	42 (51.2)	<0.0001
Primary nonfunction, ‡ n (%)	2 (2.4)	2 (2.4)	1.00
Acute rejection within 14 d, n (%)	6 (7.3)	10 (12.2)	0.28
Calcineurin inhibitor toxicity, n (%)	13 (15.9)	10 (12.2)	0.34
Serum creatinine value, median (range), mg/dL			
14 d posttransplant	4.1 (0.9–11.2)	5.1 (1.0–11.3)	0.001
1 mo posttransplant	1.7 (0.9–7.1)	2.1 (0.7–9.9)	0.017
3 mo posttransplant	1.5 (0.8–5.4)	1.5 (0.6–8.3)	0.021
Creatinine clearance, median (range), mL/min			
14 d posttransplant	23 (3–98)	13 (0–160)	<0.0001
1 mo posttransplant	46 (10–98)	35 (1–113)	0.027
3 mo posttransplant	57 (11–128)	49 (11–104)	0.117
Length of recipient hospital stay, median (range), d	17 (7–392)	19 (8–65)	0.24
Allograft survival at, n (%)			
3 mo	79 (96.3)	79 (96.3)	
1 yr	77 (93.9)	78 (95.1)	
Recipient survival at, n (%)			
3 mo	81 (98.8)	82 (100)	
1 yr	79 (96.3)	80 (97.6)	

Jochmans I et al. Ann Surg 2010;252(5):756-764.

Don’t loose sight of the basics: machine normothermic perfusion

Feasible but complicated technique: ECD kdineys

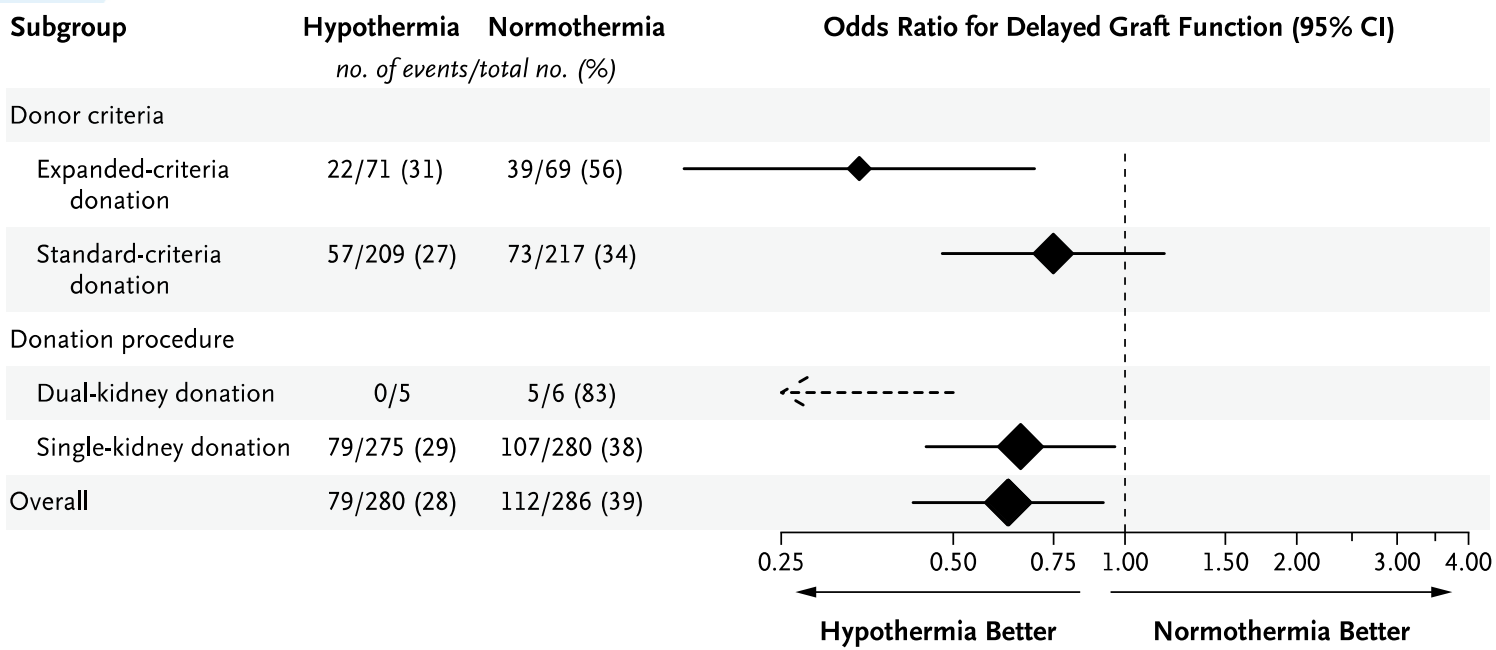




Nicholson ML et al. Am J Transpl 2013;13:1246-1252.

Don’t loose sight of the basics: donor hypothermia

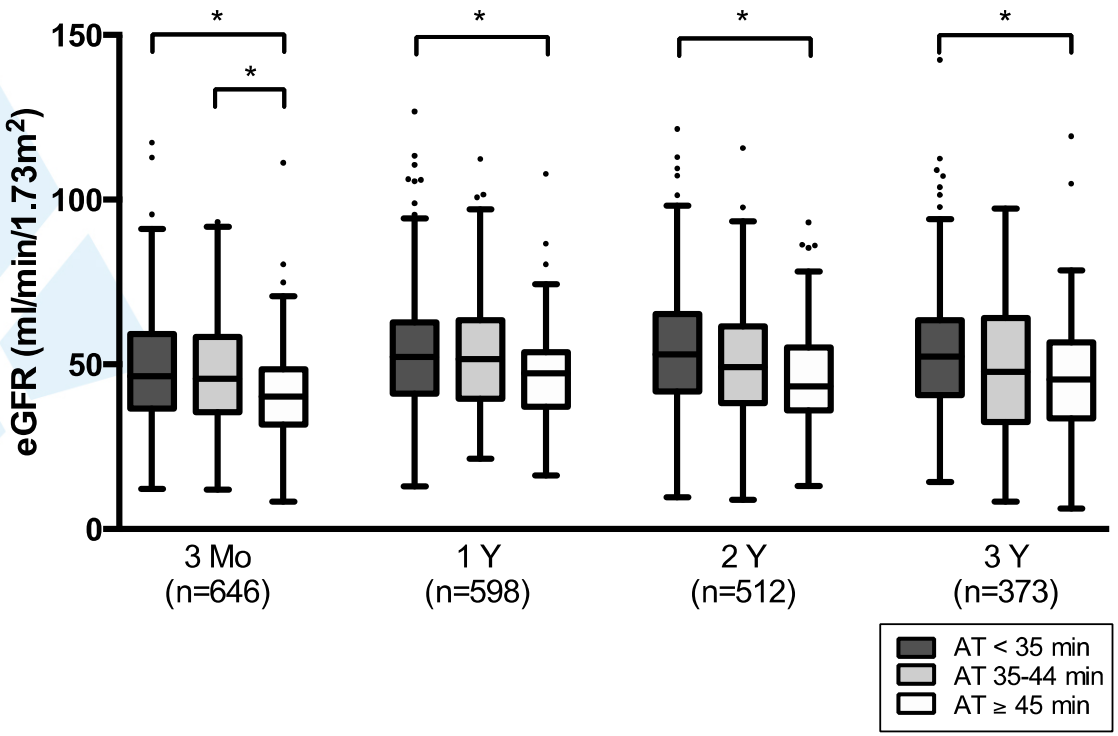
Variable	Odds Ratio for Delayed Graft Function (95% CI)	P Value
Hypothermia vs. normothermia	0.62 (0.43–0.92)	0.02
Organ-procurement organization, A vs. B	0.85 (0.57–1.28)	0.43
Standard-criteria donor vs. expanded-criteria donor	1.21 (0.69–2.13)	0.50
Creatinine level at enrollment, per 1-mg-per-deciliter increase	1.99 (1.42–2.80)	<0.001
Donor age, per 1-yr increase	1.04 (1.02–1.05)	<0.001
Kidney cold-ischemia time, per 1-hr increase	1.03 (1.00–1.05)	0.04



Niemann CU et al. N Engl J Med 2015;373:405-414.

Don’t loose sight of the basics: anastomosis time

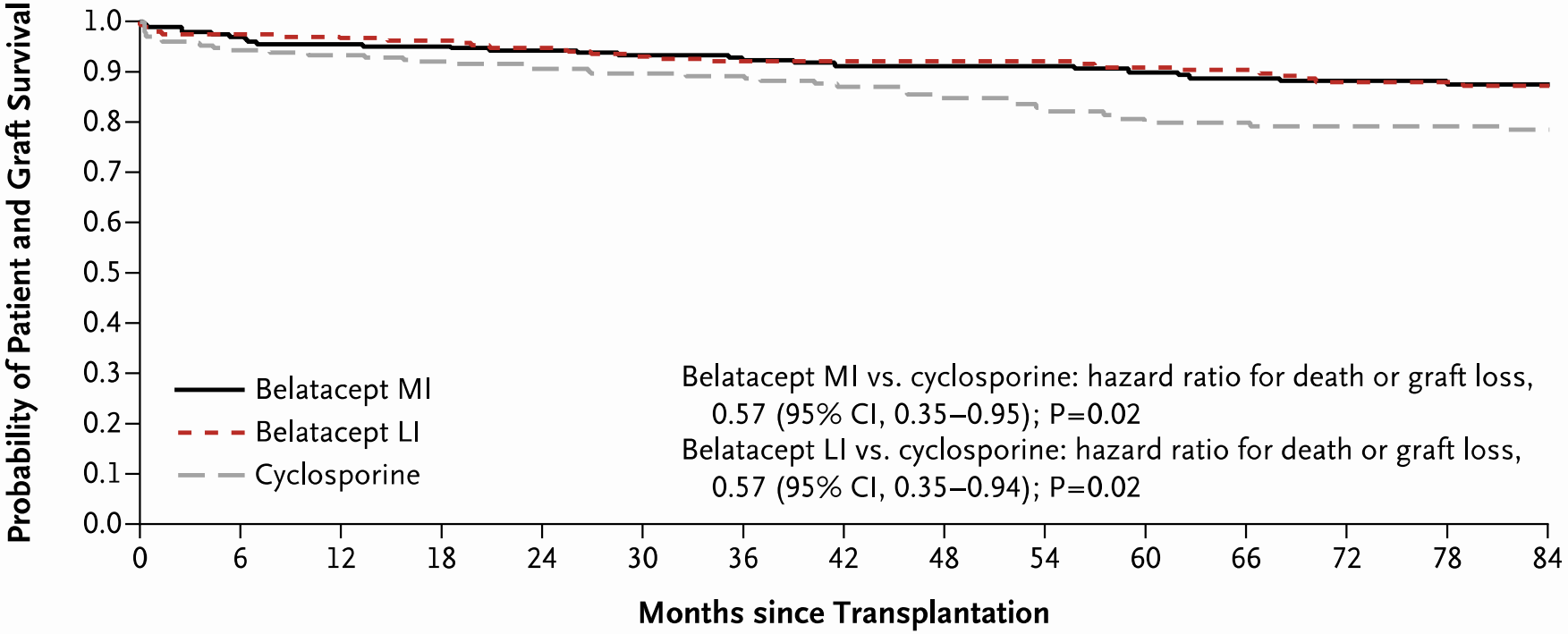
	OR	95% CI	p value
Year of transplant (y)	0.88	0.80–0.97	**0.008**
Donor age (y)	0.99	0.97–1.01	0.44
Donor criteria (SCD vs ECD)	1.70	0.87–3.31	0.12
Recipient age (y)	1.02	0.99–1.04	0.13
Recipient BMI (kg/m^2)	1.06	1.01–1.11	**0.015**
Total number of HLA mismatch	1.13	0.96–1.35	0.15
Cold ischemia time (h)	1.07	1.02–1.13	**0.006**
Anastomosis time (min)	1.05	1.02–1.07	**0.001**



Heylen L et al. Am J Transpl 2015;15:2900-2907.

Better immunosuppressive drugs?

Belatacept: 7 year results – patient and graft survival

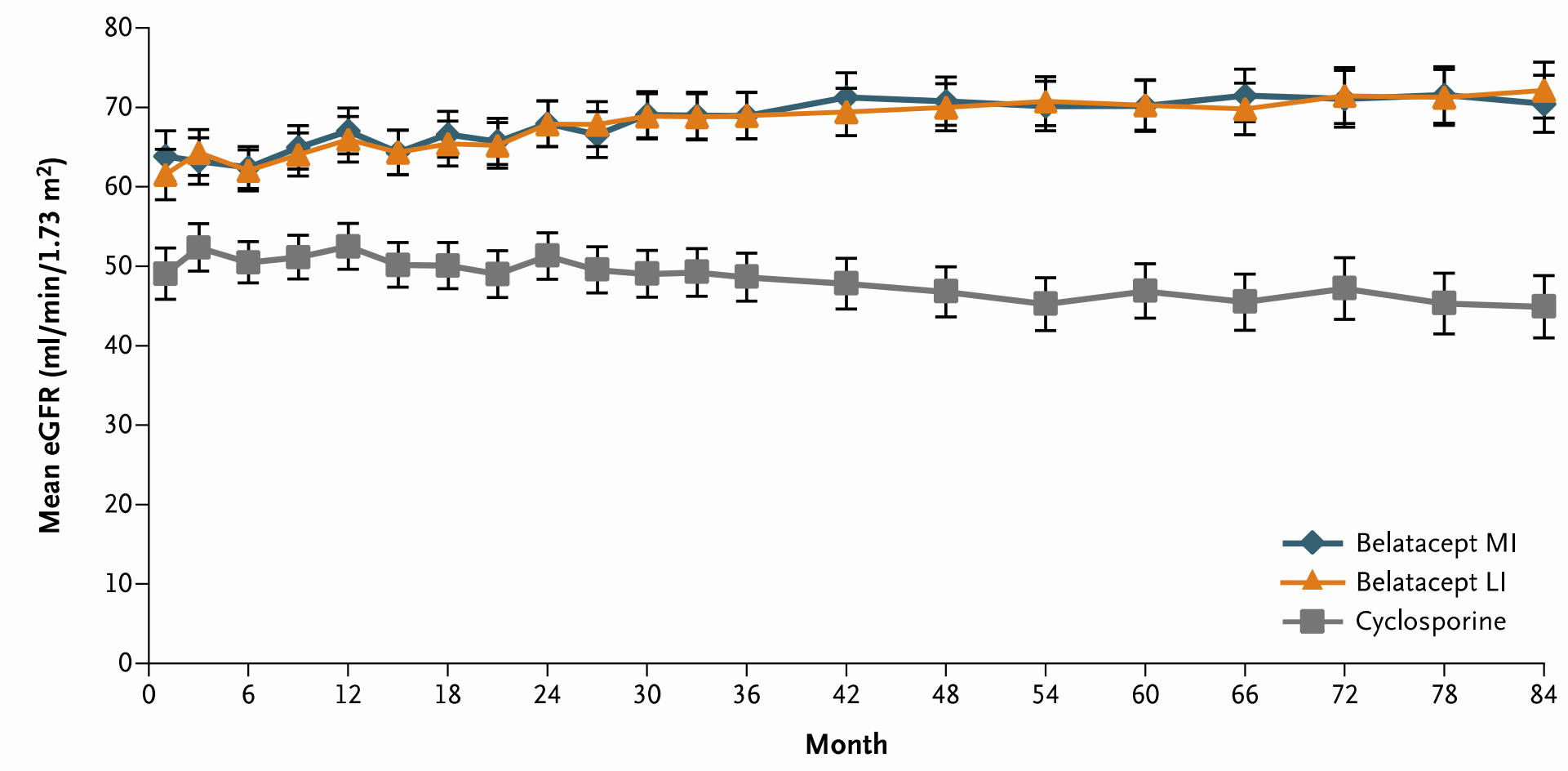


No. at Risk															
Belatacept MI	219	212	208	206	204	202	199	153	151	149	146	142	135	131	128
Belatacept LI	226	220	218	216	213	209	204	165	161	159	152	151	142	139	137
Cyclosporine	221	208	206	202	199	197	186	137	123	117	112	107	102	100	92

Vincenti F et al. N Engl J Med 2016;374:333-343.

Better immunosuppressive drugs?

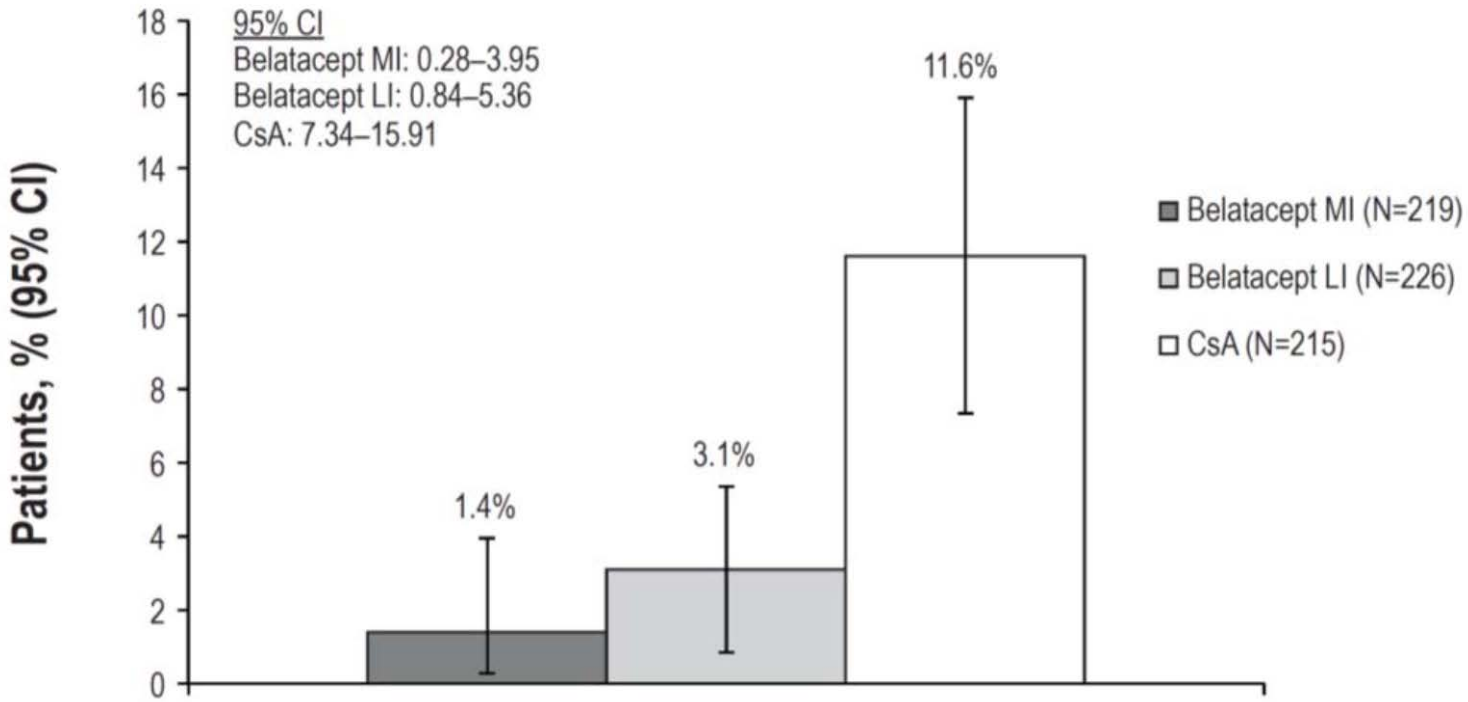
Belatacept: 7 year results – kidney function



Vincenti F et al. N Engl J Med 2016;374:333-343.

Better immunosuppressive drugs?

Belatacept: 7 year results – development of DSAs



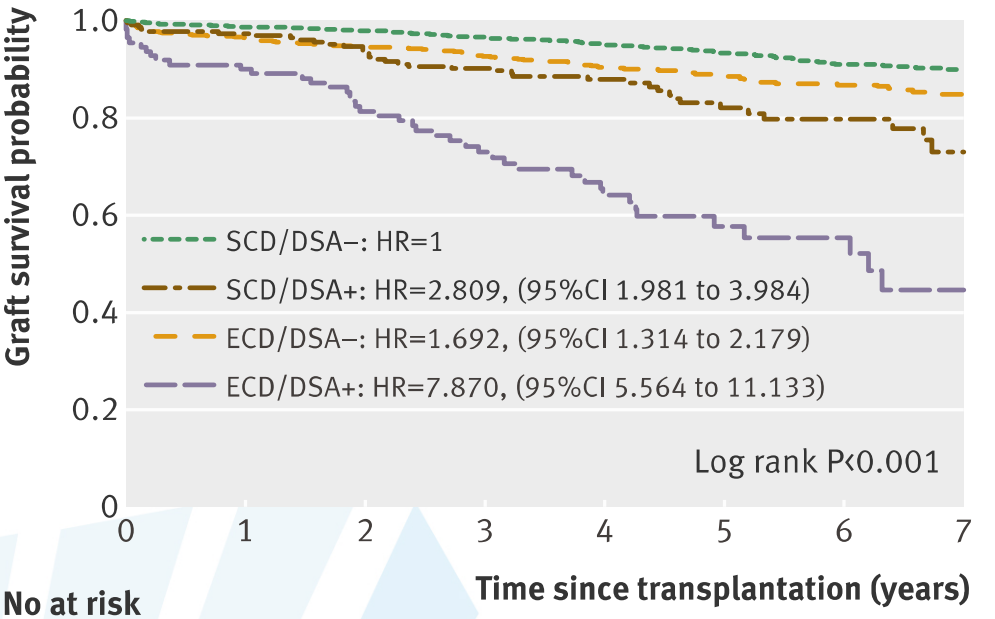
Specificity	Belatacept MI	Belatacept LI	CsA
Total, n	3	7	25
Class I DSA, n	1	3	7
Class II DSA, n	2	4	14
Class I and II DSA, n	0	0	4

Vincenti F et al. N Engl J Med 2016;374:333-343.

Overview

- Transplantation in 2016
- Non-invasive diagnosis - biomarkers
- Humoral rejection takes center stage
- Don’t loose sight of the basics
  - Non-adherence
  - Machine perfusion
  - Hypothermia
  - Anastomosis time
  - Better immunosuppressive drugs
- Alternatives for classic kidney transplantation

Alternatives for classic kidney transplantation: ECD kidneys



No at risk

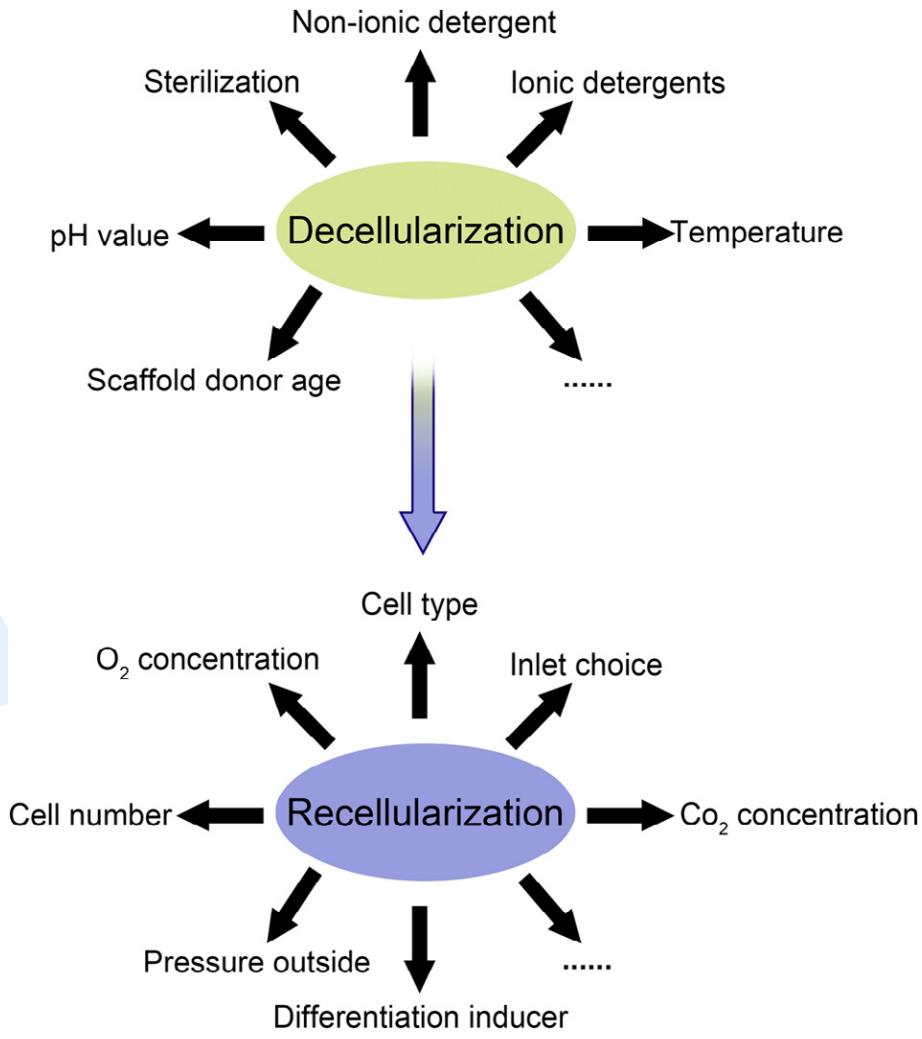
SCD/DSA–	1622	1591	1552	1419	1216	962	708	504
SCD/DSA+	225	219	208	175	133	77	50	22
ECD/DSA–	806	756	723	641	511	393	275	175
ECD/DSA+	110	98	83	63	47	26	17	4

	No of patient/events	Hazard ratio (95% CI)	P	Internal validation hazard ratio 95% CI, BCA
Expanded criteria donor				
No	1835/187	1	<0.001	—
Yes	855/138	1.842 (1.467 to 2.311)		(1.463 to 2.275)
Cold ischaemia time				
<12 h	670/44	1	0.017	—
12-24 h	1514/198	1.457 (1.042 to 2.039)		(1.042 to 2.093)
≥24 h	506/83	1.727 (1.185 to 2.517)		(1.195 to 2.506)
Graft rank				
1	2278/241	1	0.002	—
>1	412/84	1.544 (1.168 to 2.042)		(1.129 to 2.046)
No of HLA A/B/DR mismatches	2690/325	1.095 (1.013 to 1.184)	0.022	(1.013 to 1.182)
Anti-HLA DSA on day 0				
No	2364/241	1	<0.001	—
Yes	326/84	2.988 (2.265 to 3.941)		(2.198 to 3.940)

Aubert O et al. BMJ 2015;251:h3557.

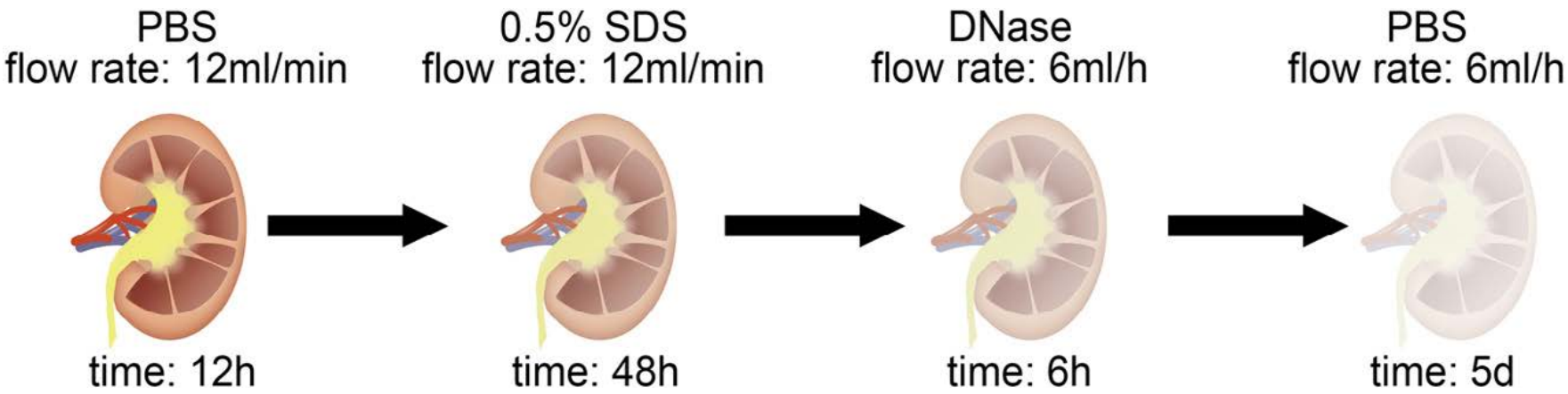
Alternatives for classic kidney transplantation

- Kidney bioengineering - regenerative medicine
  - Decellularization and recellularization scaffolds
  - Use for discarded kidneys
  - 3D printing?



Lin YQ et al. Cytotherapy 2016;18:186-197.

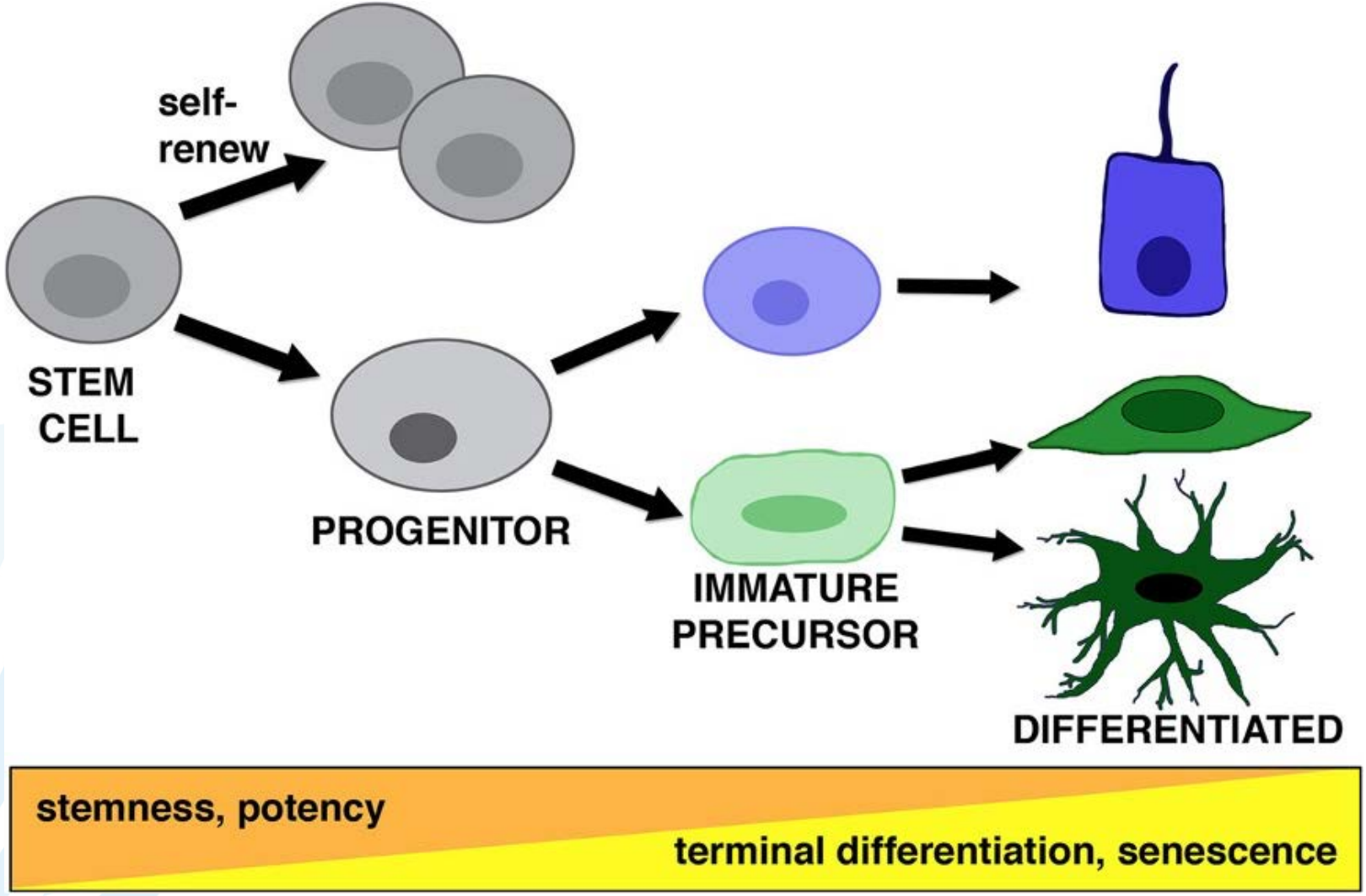
Alternatives for classic kidney transplantation



Author	Cell type	Cell numbers	Inlet choice	Basic recellularization result	Reference
Ross et al.	Mice ESC	Not mentioned	Antegrade through the artery or retrograde through the ureter.	Primitive precursor cells populated and proliferated within the glomerular, vascular and tubular structures.	[28]
Caralt et al.	RCTE	40×10^6	Renal artery.	Resided on the basement membrane and formed what appear to be tubular structures.	[14]
Song et al.	HUVEC	$50.67 \times 10^6 \pm 12.84 \times 10^6$	Arterial cannula.	Grafts produced rudimentary urine *in vitro* and *in vivo*.	[29]
Lam et al.	hPSC	Not mentioned.	Not mentioned.	hPSC form tubules that express proximal tubular markers.	[86]
Song et al.	iPSC	Not mentioned.	Not mentioned.	The first report of the directed differentiation of iPS to generate kidney cells with podocyte features.	[85]

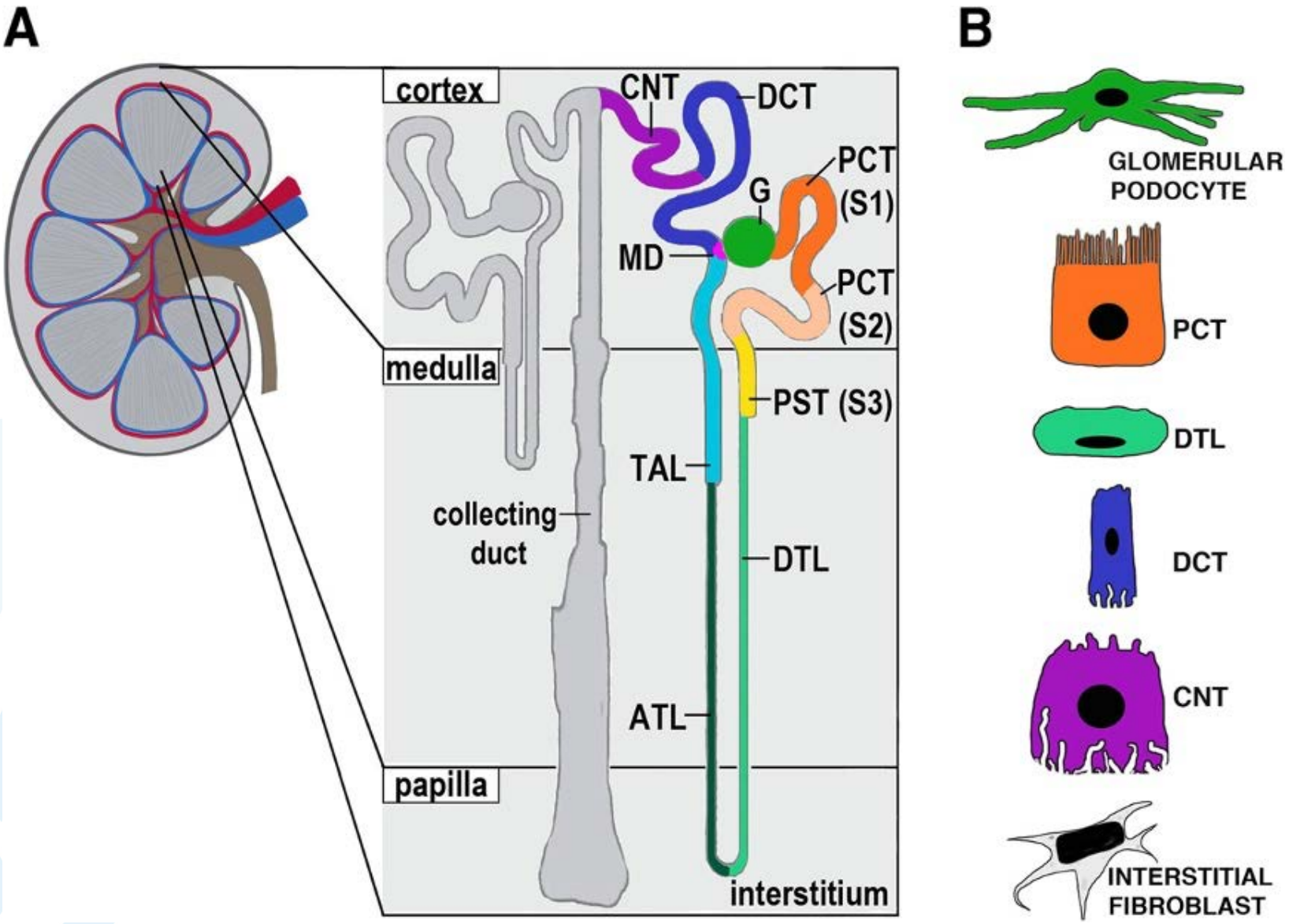
Lin YQ et al. Cytotherapy 2016;18:186-197.

Alternatives for classic kidney transplantation



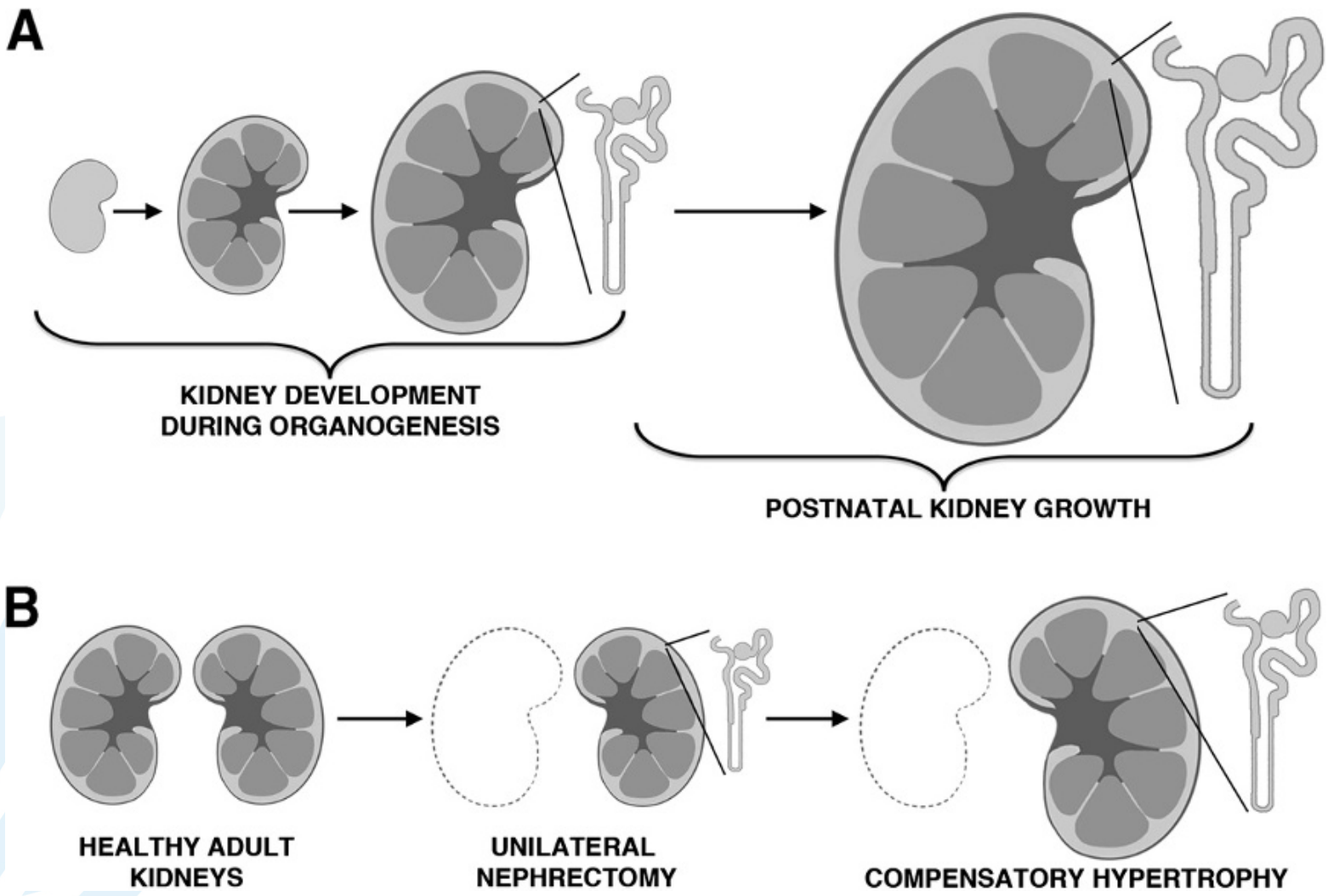
Li Y et al. Clinical and translational Medicine 2013;2:11-16.

Alternatives for classic kidney transplantation



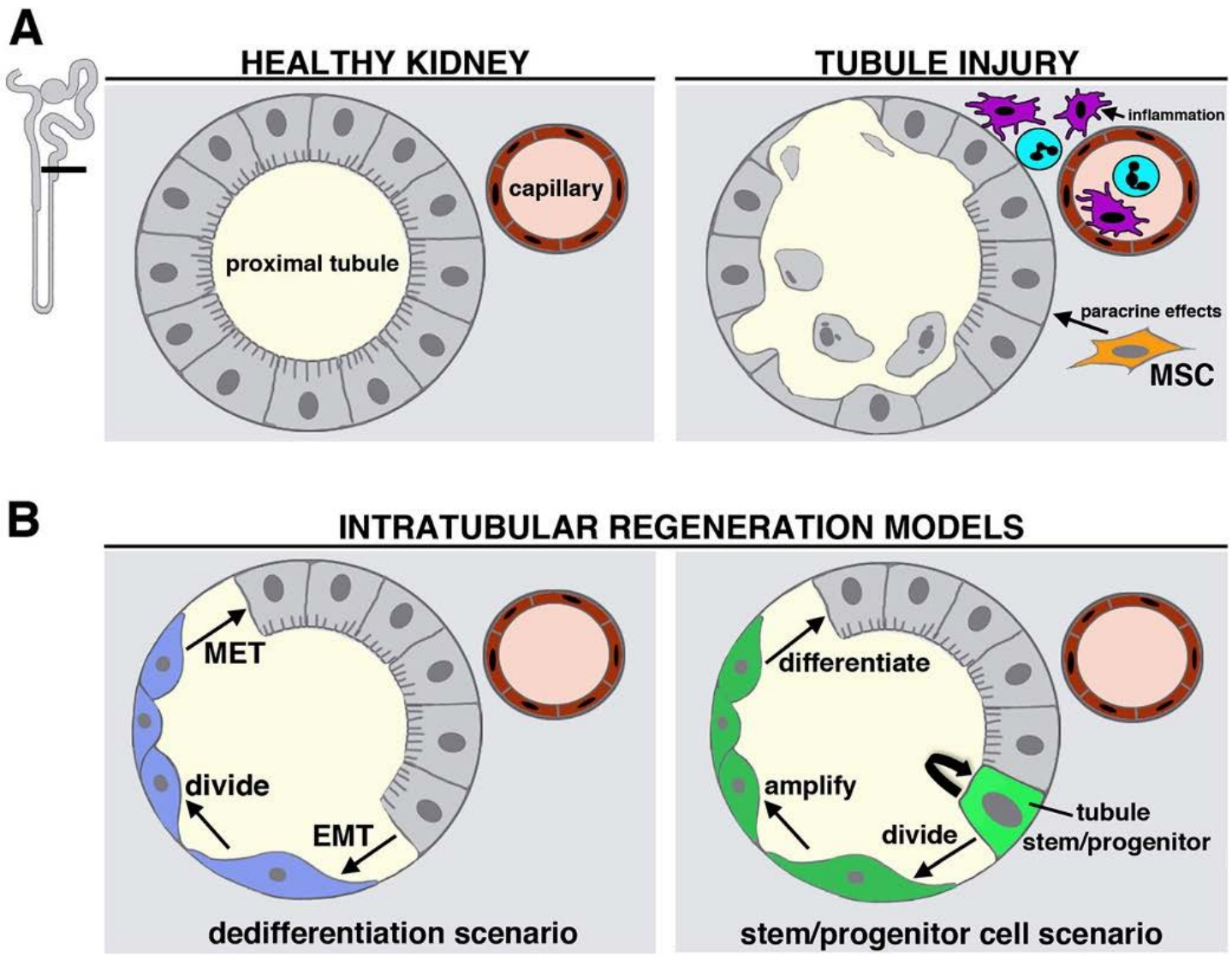
Li Y et al. Clinical and translational Medicine 2013;2:11-16.

Alternatives for classic kidney transplantation



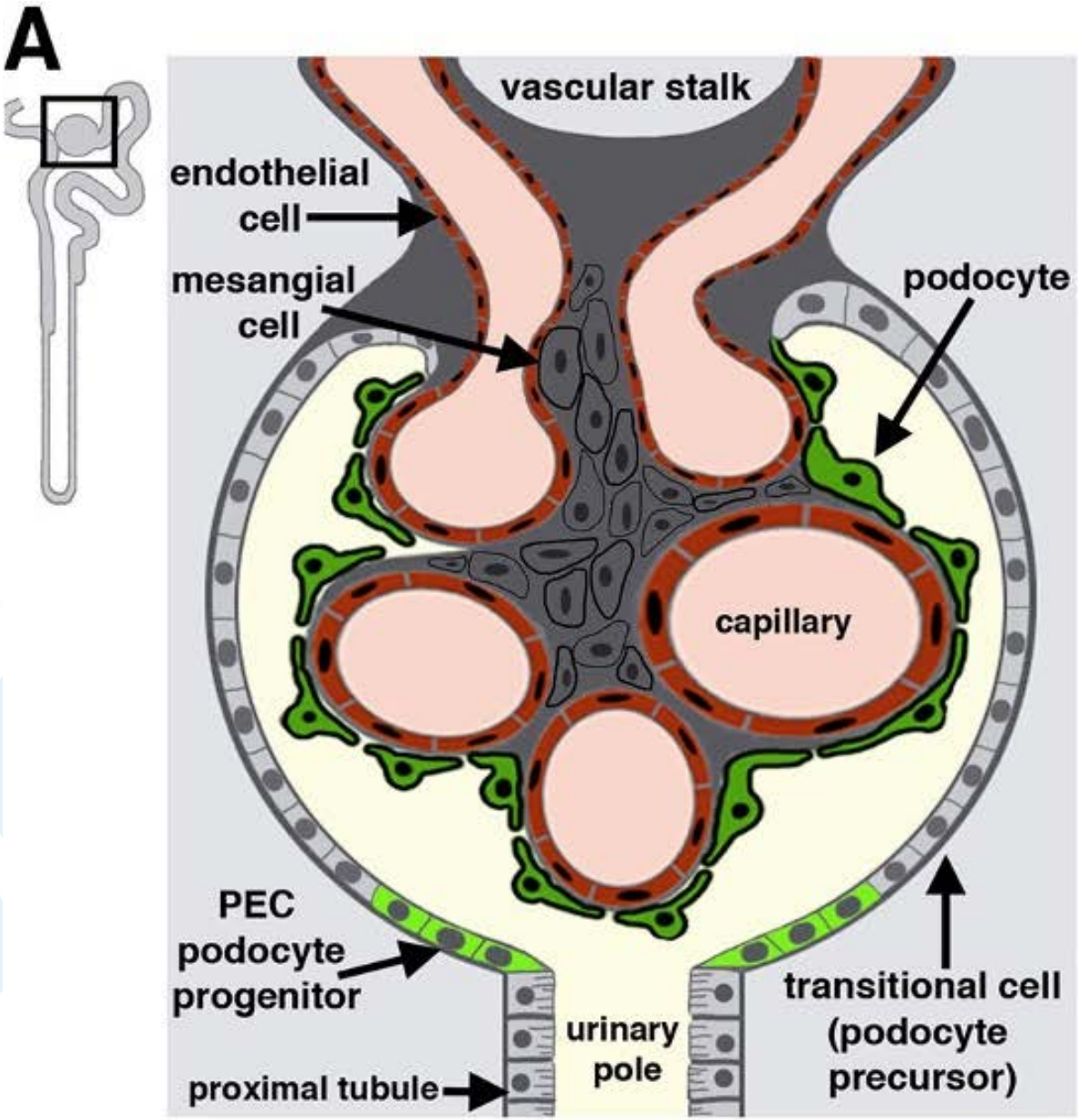
Li Y et al. Clinical and translational Medicine 2013;2:11-16.

Alternatives for classic kidney transplantation



Li Y et al. Clinical and translational Medicine 2013;2:11-16.

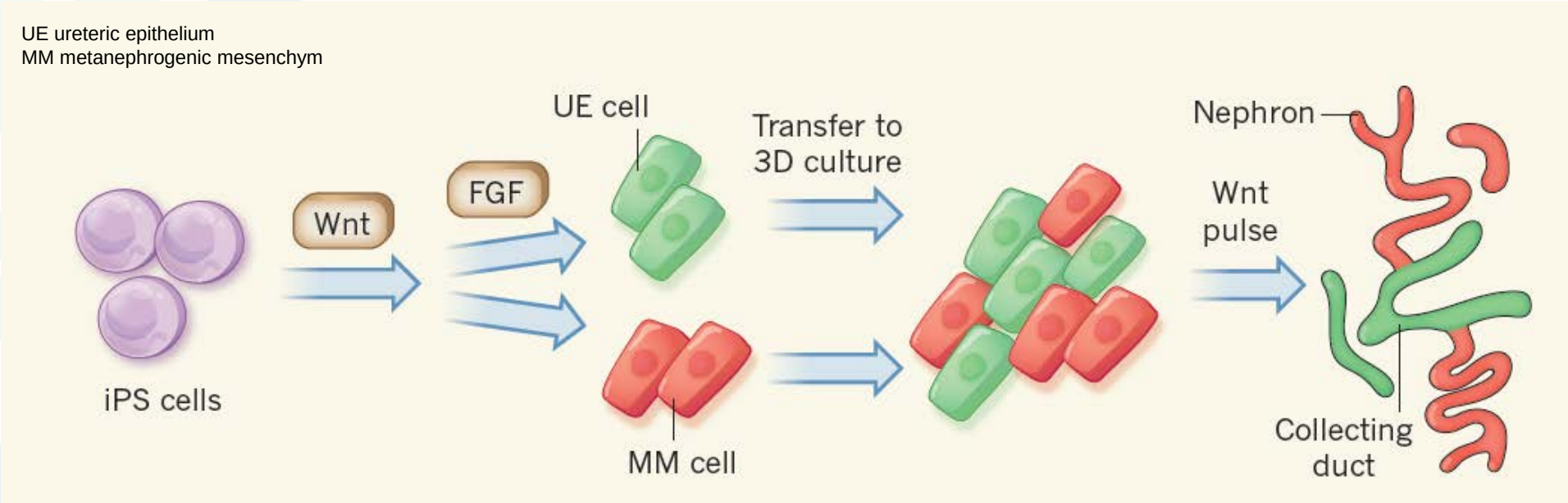
Alternatives for classic kidney transplantation



Li Y et al. Clinical and translational Medicine 2013;2:11-16.

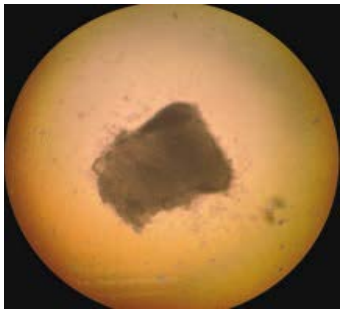
Alternatives for classic kidney transplantation

- Kidneys in a petridish
  - Stem cells must be persuaded to develop into kidney cells rather than those of other tissues
  - Thereafter, cells must be encouraged to build the intricate complex anatomy of the kidney
  - The cultured kidney must be coaxed to grow and function in a host patient
- Remarks
  - Organoids
  - Most interestingly for drug research



Davies JA. Nature 2015;526:512-513.

Alternatives for classic kidney transplantation



Takasato M et al. Nature 2015;526:564-568.

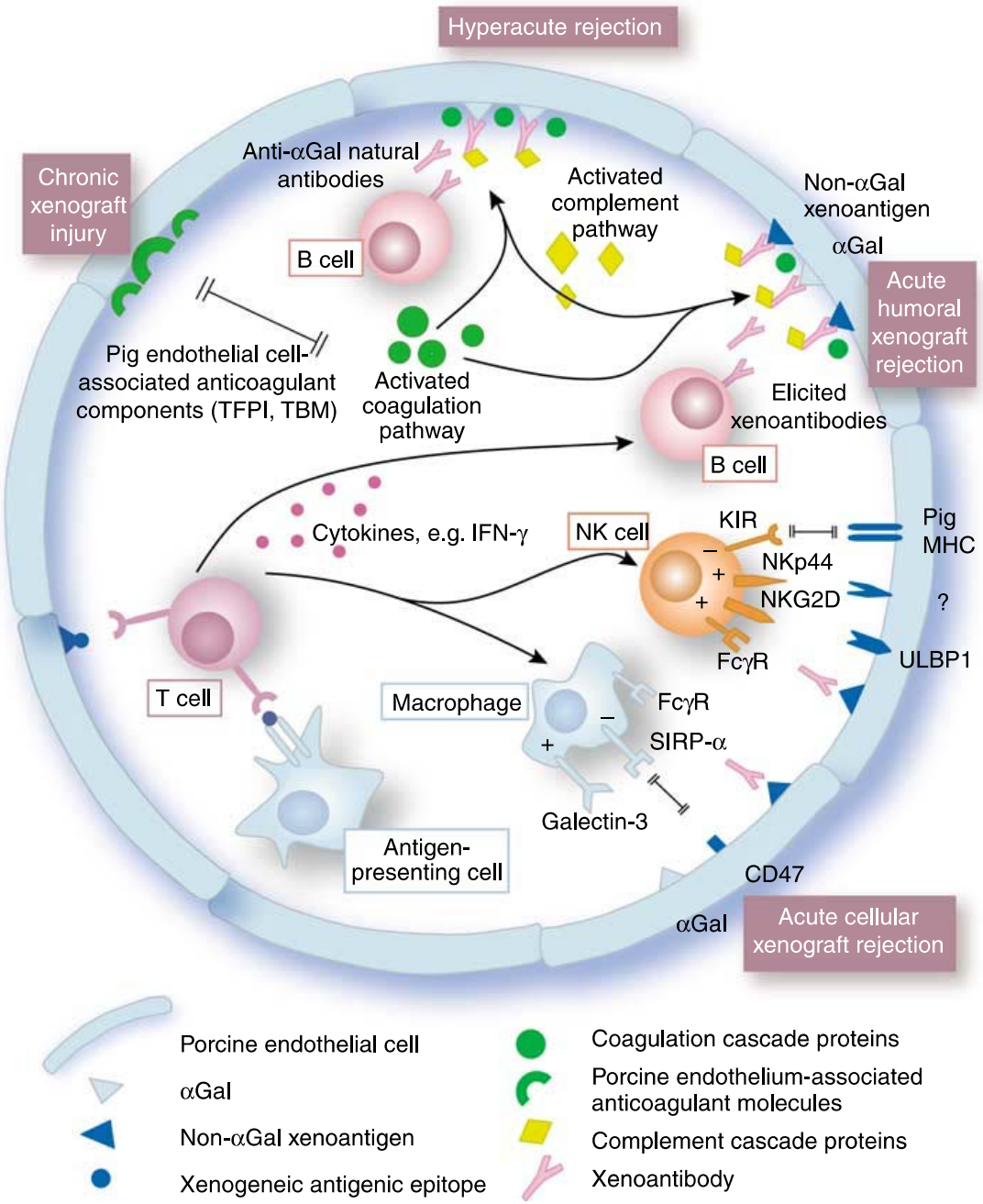
Alternatives for classic kidney transplantation

- Xenotransplantation
  - Unattainable dream or reality in the (near) future?
  - Barriers: immunological and non-immunological

	Pig	Baboon
Availability	Unlimited	Limited
Breeding potential	Good	Poor
Period to reproductive maturity	4–8 months	3–5 years
Length of pregnancy	114 ± 2 days	173–193 days
Number of offspring	5–12	1–2
Growth	Rapid (adult human size within 6 months)[a]	Slow (9 years to reach maximum size)
Size of adult organs	Adequate	Inadequate[†]
Cost of maintenance	Significantly lower	High
Anatomical similarity to humans	Moderately close	Close
Physiological similarity to humans	Moderately close	Close
Relationship of immune system to humans	Distant	Close
Knowledge of tissue typing	Considerable (in selected herds)	Limited
Necessity for blood type compatibility with humans	Probably unimportant	Important
Experience with genetic engineering	Considerable	None
Risk of transfer of infection (xenozoonosis)	Low	High
Availability of specific pathogen-free animals	Yes	No
Public opinion	More in favor	Mixed

Cooper DKC et al. Int J Surg 2015;23:205-210.

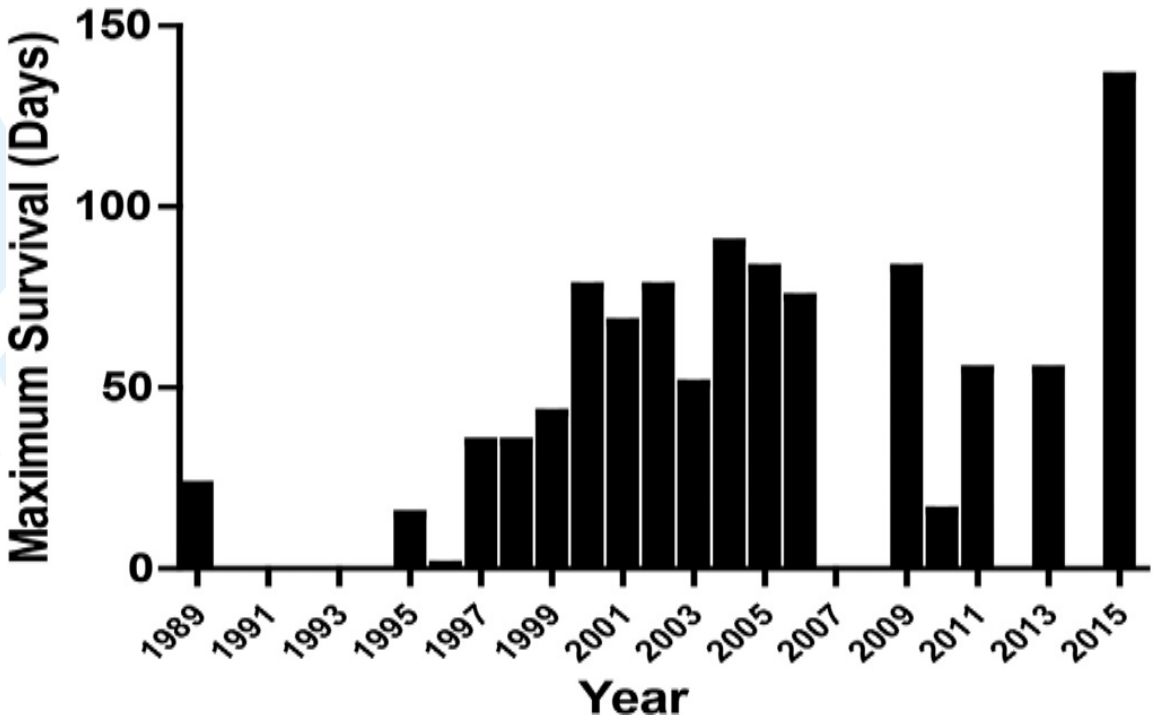
Alternatives for classic kidney transplantation



Sprangers B et al. Kidney Int 2008;74:14-21.

Alternatives for classic kidney transplantation

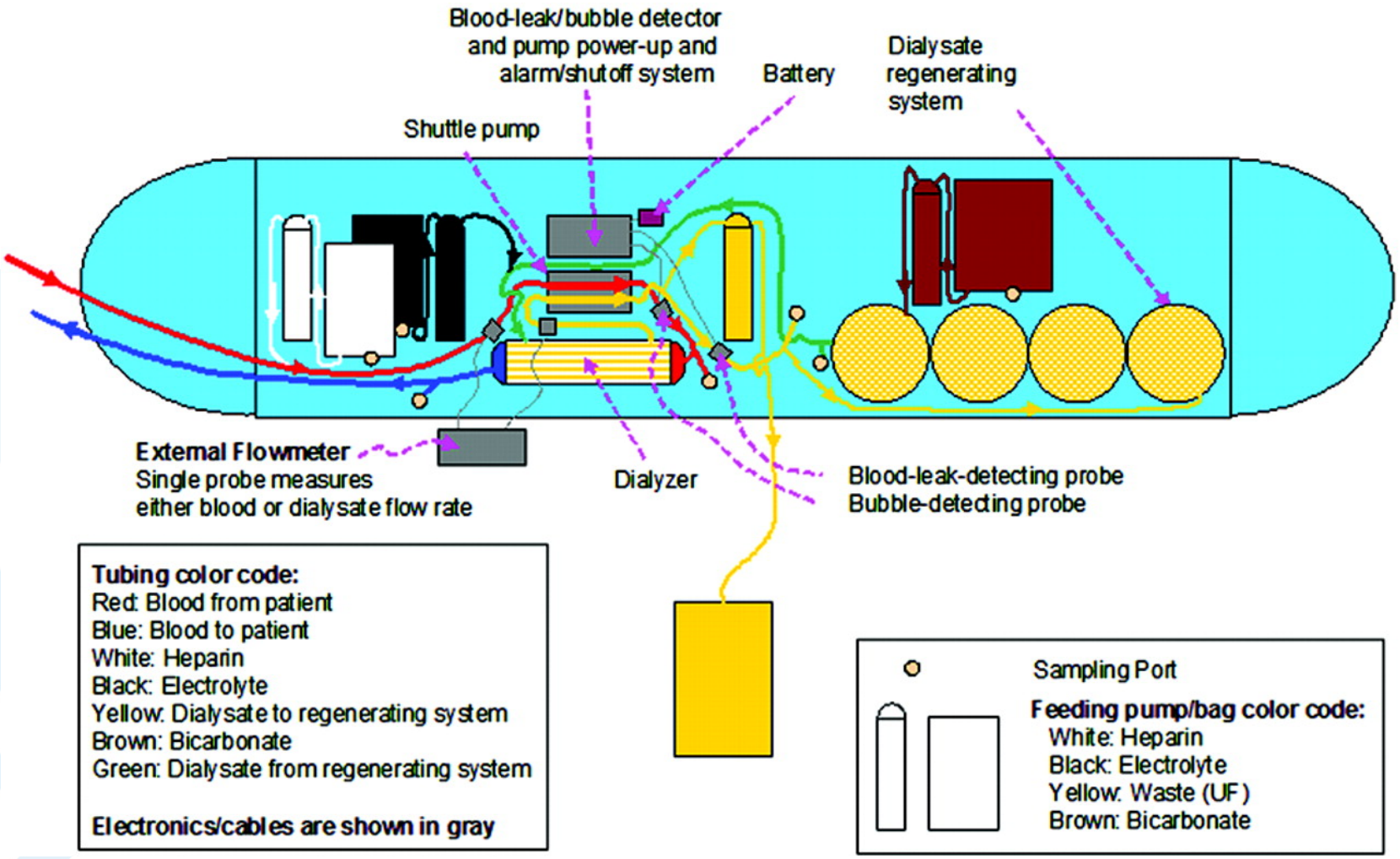
	Human	GTKO[b] Pig
Sodium (mmol/L)	136–146	144
Potassium (mmol/L)	3.5–5.0	5.3
Chloride (mmol/L)	95–110	103.0
Calcium (mg/dL)	8.4–10.2	10.8
Phosphorus (mg/dL)	2.5–4.5	8.8
CO_2 (mmol/L)	21–32	28.1
Urea (mg/dL)	5.0–20.0	12.8
Creatinine (mg/dL)	0.6–1.1	1.1



Ekser B et al. Int J Surg 2015;23:199-204.

Alternatives for classic kidney transplantation

- Wearable kidneys
  - From WAK to WUK



Gura V et al. Clin J Am Soc Nephrol 2009;4:1441-1448.

Conclusion

Transplantatie: wat hebben we geleerd over de uitdagingen van morgen?

- Het wordt nog ingewikkelder
- Verlies het voor de hand liggende niet uit het oog

Regenerative medicine

- Nog een lange weg te gaan maar grote investeringen worden gedaan

Xenotransplantatie

- Eeuwige belofte?

Dank!