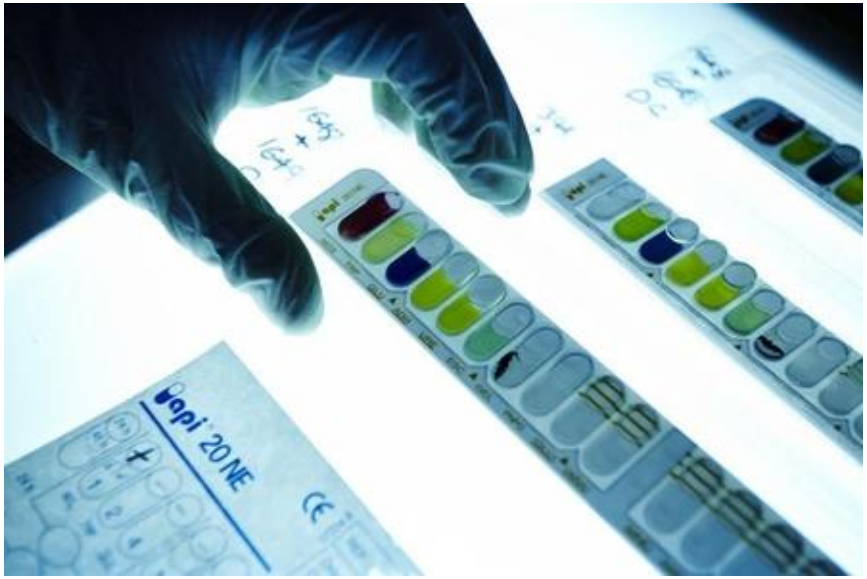

Assessment of Rejection

Uwe Schulz

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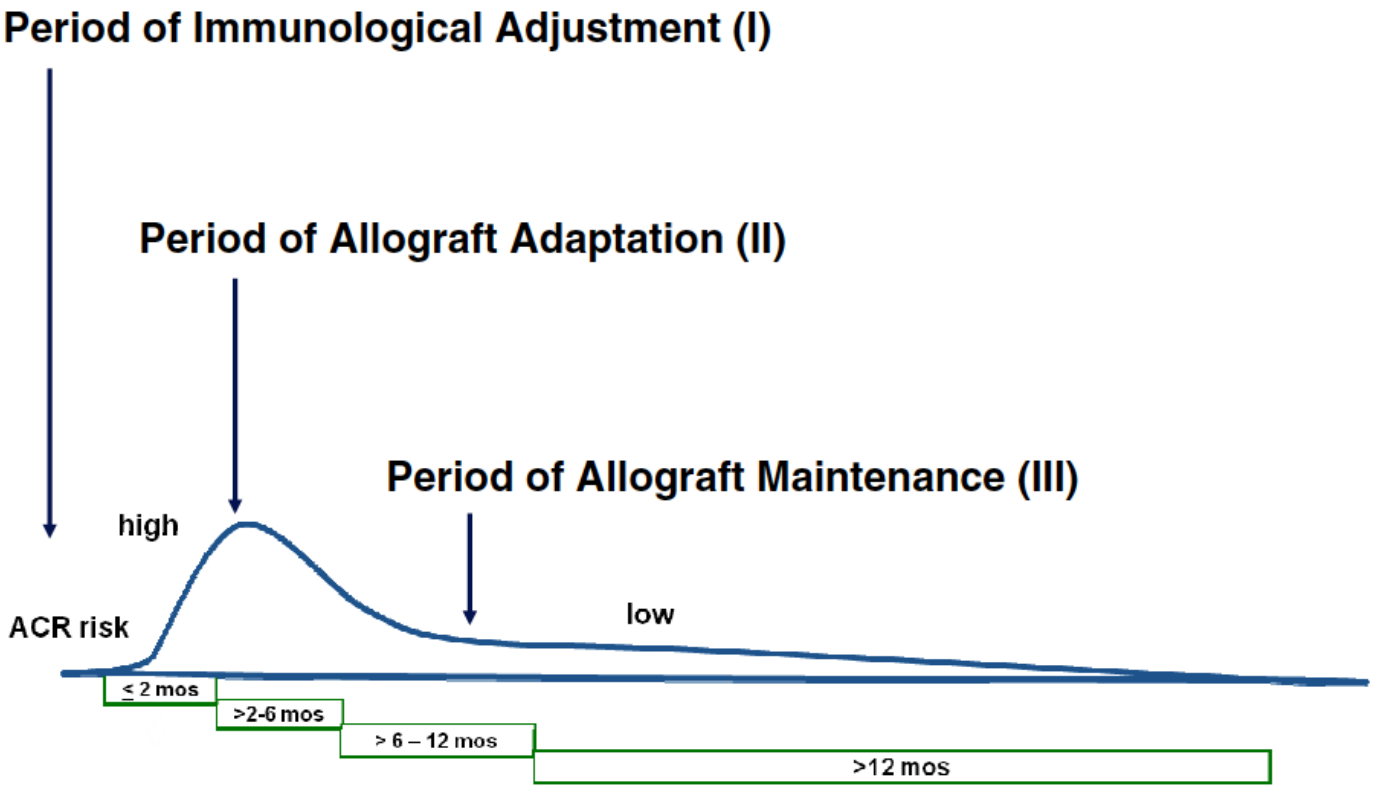
I.	II.	III.	IV.
I have received (a) research grant(s) / in kind support	I have been a speaker or participant in accredited CME/CPD ...	I have been a consultant / strategic advisor etc. ...	I am a holder of (a) patent / shares / stocks or ownership...
A	**A**	**A**	**A**
... from current sponsor(s)	... from current sponsor(s)	... for current sponsor(s)	... related to presentation
YES:	NO: X	YES:	NO: X	YES:	NO: X	YES:	NO: X
B	**B**	**B**	**B**
... from any institution	... from any institution	... for any institution	... not related to presentation
YES: X	NO:	YES: X	NO:	YES: X	NO:	YES:	NO: X

SCORE: 8

The role of biomarkers: Cornerstones

- identify patients at risk for acute rejection or infection
- manage the timing and rate of immunosuppressant weaning
- identify candidates for minimization of immunosuppressive therapy
- sequential monitoring may allow maintenance of an individualized immunosuppressive regimen

PERIODS AFTER HEART TRANSPLANTATION



I. Intense Vigilence	II. Gene-based Risk Stratification	III. Clinical and Functional Evaluation

From Mehra et al. 2010

Race and ethnic differences in the epidemiology and risk factors for graft failure after heart transplantation

Disruptions in the Supply of Medications Used in Transplantation: Implications and Management Strategies for the Transplant Clinician

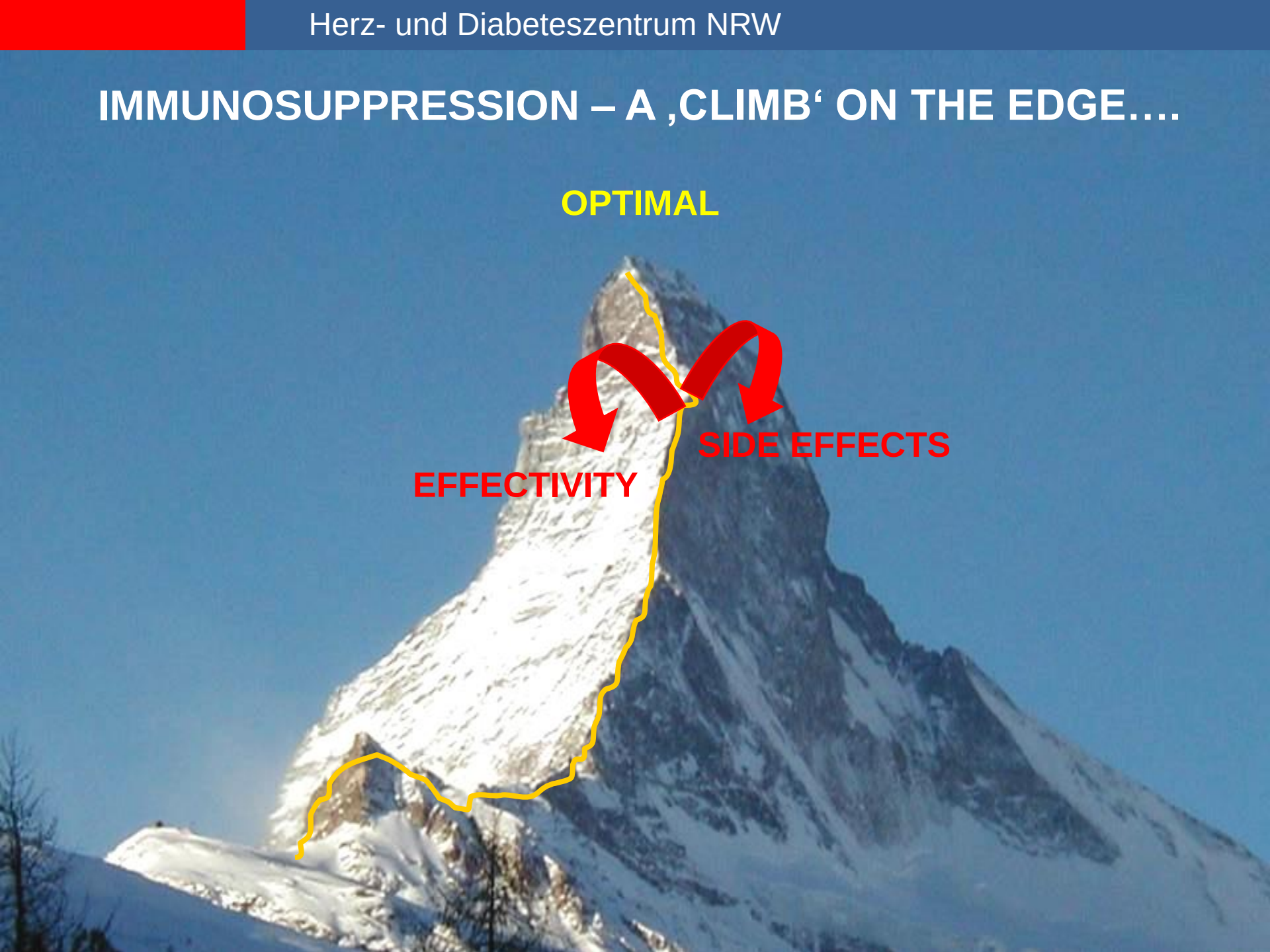
Solid-Organ Transplantation in Older Adults: Current Status and Future Research

Pre-transplant immune state defined by serum markers and alloreactivity predicts acute rejection after living donor kidney transplantation

Metabolic consequences of modern immunosuppressive agents in solid organ transplantation

Utility of immune monitoring in heart transplant recipients on everolimus-based immune suppression

IMMUNOSUPPRESSION – A ‚CLIMB' ON THE EDGE….



INTRODUCTION

- **Endomyocardial biopsy (EMB)** is still considered the gold standard for graft rejection surveillance
- **HOWEVER:**
  - Invasive and uncomfortable for patients
  - Risk for significant morbidity
  - Inter-pathologist variance *(Crespo-Leiro 2012)*

→ ***1. Less invasive and reliable alternative desirable***
2. Identification of patients who require EMB

EMB-ANALYSIS – GOLDSTANDARD?

Concordance Among Pathologists in the Second Cardiac Allograft Rejection Gene Expression Observational Study (CARGO II)

Maria G. Crespo-Leiro,[1] Andreas Zuckermann,[2] Christoph Bara,[3] Paul Mohacsi,[4] Uwe Schulz,[5] Andrew Boyle,[6] Heather J. Ross,[7] Jayan Parameshwar,[8] Michael Zakliczyński,[9] Roberto Fiocchi,[10] Joerg Stypmann,[11] Daniel Hoefer,[12] Hans Lehmkuhl,[13] Mario C. Deng,[14] Pascal Leprince,[15] Gerald Berry,[16] Charles C. Marboe,[14] Susan Stewart,[8] Henry D. Tazelaar,[17] Helen M. Baron,[18] Ian-Charles Coleman,[1] and Johan Vanhaecke[19]

(*Transplantation* 2012;94: 1172–1177)

TABLE 1. Positive grade-specific agreement, negative grade-specific agreement, and overall (all-grade) agreement between panel pathologists on the ISHLT 2004 grade of EMB samples

	Grade 0R		Grade 1R		Grade ≥2R		
Pathologists	PA	NA	PA	NA	PA	NA	Overall
P1–P2	60.8 (55.3–66.1)	58.3 (52.7–63.8)	40.7 (35.1–46.4)	56.4 (51.5–61.3)	17.6 (9.5–26.6)	88.1 (85.3–90.8)	64.8 (60.6–69.0)
P1–P3	57.4 (52.1–62.8)	52.7 (47.2–58.4)	40.6 (34.8–46.6)	58.3 (53.4–63.4)	27.4 (16.2–38.9)	90.2 (87.4–92.9)	64.6 (60.5–69.0)
P1–P4	57.3 (51.9–62.7)	53.8 (47.9–59.4)	43.7 (37.7–49.5)	57.6 (52.5–62.7)	28.0 (15.7–40.5)	92.2 (89.6–94.5)	66.0 (61.7–70.2)
P2–P3	71.3 (66.6–75.7)	60.6 (54.8–66.3)	53.7 (47.7–59.6)	70.1 (65.6–74.6)	21.2 (8.0–35.5)	95.0 (93.1–96.8)	76.5 (72.9–79.9)
P2–P4	68.6 (64.1–73.3)	55.3 (49.4–61.5)	50.4 (44.2–56.8)	69.0 (64.6–73.6)	37.0 (19.2–55.6)	96.7 (95.1–98.1)	75.3 (71.6–79.1)
P3–P4	71.6 (66.9–76.1)	57.9 (51.5–64.1)	53.0 (46.3–59.6)	72.4 (67.9–76.8)	34.5 (17.4–52.4)	96.0 (94.3–97.7)	77.3 (73.6–81.0)
P1	58.5	55.0	41.6	57.4	23.7	90.1	65.1
P2	67.1	58.1	47.9	65.1	22.4	93.3	72.2
P3	67.1	56.9	48.8	67.0	27.4	93.8	73.0
P4	66.2	55.5	48.7	66.5	32.1	95.0	73.0
Whole panel	64.8	56.4	46.6	64.0	25.8	93.1	70.8

Top panel: pairwise agreement for each pair of pathologists. Middle panel: average agreement of each pathologist with the other three. Bottom panel: average over all pathologist pairs. Agreement values are expressed as percentages; in parentheses, estimated 95% confidence intervals.
PA, positive agreement; NA, negative agreement.

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UK RUB UNIVERSITÄTS RUHR-UNIVERSITÄT

EMB-ANALYSIS – GOLDSTANDARD?

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(*Transplantation* 2012;94: 1172–1177)

TABLE 3. Agreement (%) between panel and local centers on ISHLT 2004 grades

Grade	PA	NA
0R	62.1 (58.1–66.1)	58.7 (54.5–62.9)
1R	50.0 (45.5–54.5)	61.0 (57.2–64.8)
≥2R	28.4 (18.4–38.8)	94.0 (92.3–95.5)
Overall	70.7 (67.7–73.7)	

In parentheses, estimated 95% confidence intervals.
PA, positive agreement; NA, negative agreement.

ALLOMAP®

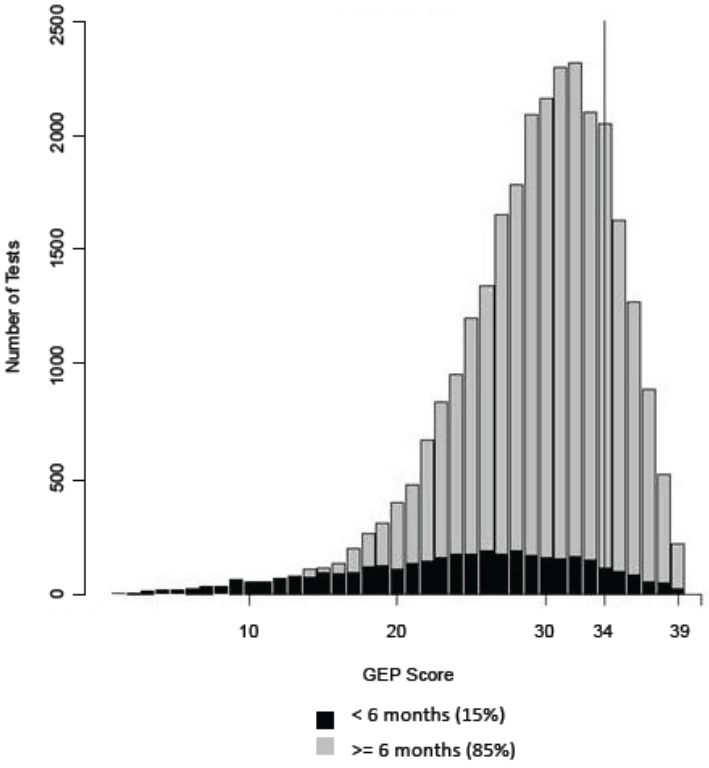
- **AlloMap®: profiling of peripheral blood mononuclear cell (PBMC) gene expression**
- **Yields score between 0-40 from single blood sample**
- **Designed to identify patients at risk for graft rejection** *(Deng 2006)*

CARGO I

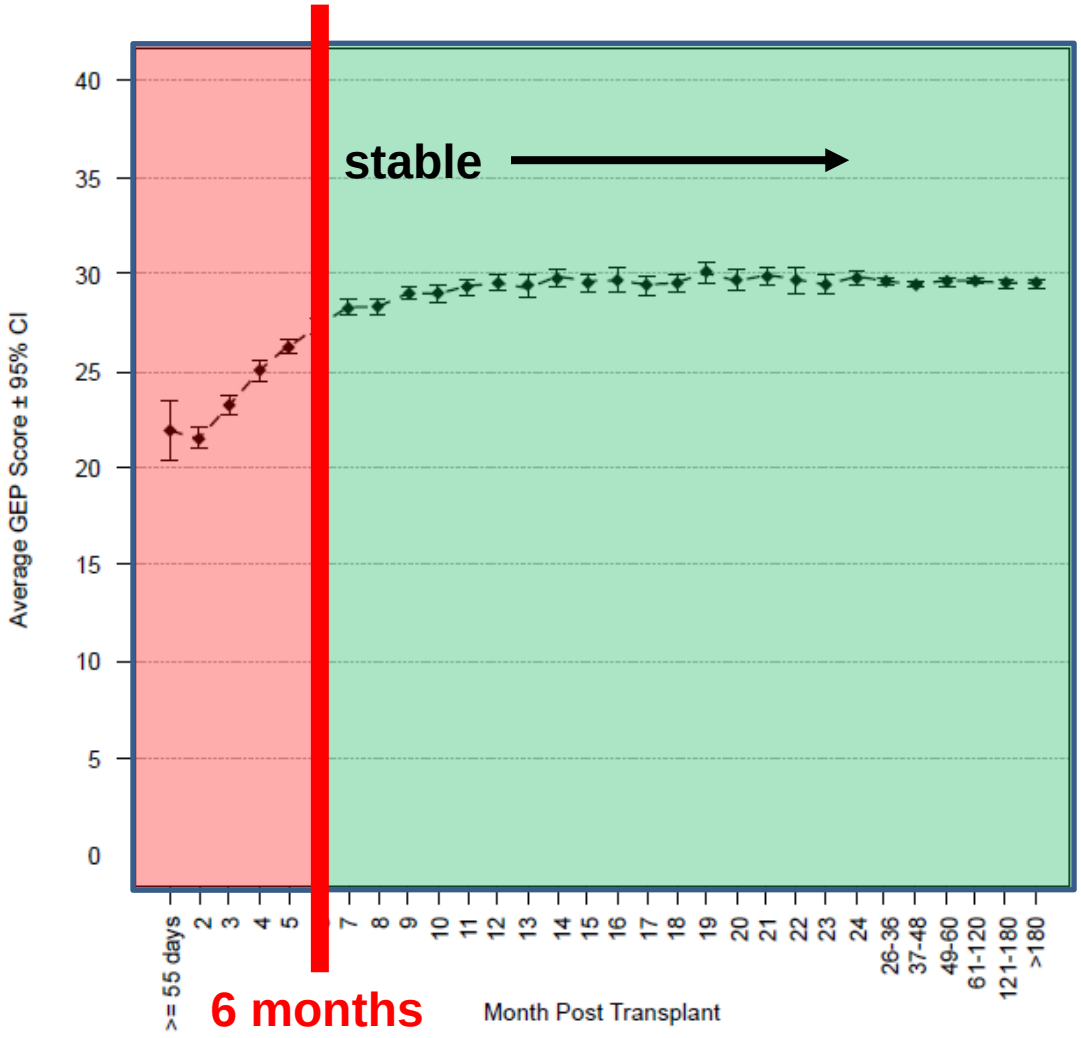
- **AlloMap accurately detected absence from rejection ISHLT ≥3 (p=0.0018)**
- **Agreement of 84% with rejection ISHLT ≥3**
- **>1 year post HTx and AlloMap <34: NPV >99%**

→ **probability for rejection at the time of AlloMap scoring** *(Deng et al. 2006)*

Effect of time on AlloMap™ performance



Month Post Transplant	Percent of Tests with GEP score < 34
< 6 months	89%
≥ 6 months	77%



(Austin et al. 2013)

Effect of time of AlloMap™ performance

Table 2: AlloMap Testing Clinical Performance Characteristics*+

Post-Transplant Period >2 - 6 months (n=166 samples)			AlloMap Score**	Post-Transplant Period >6 months (n=134 samples)		
NPV <3A(2R) ± SE	% Pts Below	PPV ≥3A(2R) ± SE		NPV <3A(2R) ± SE	% Pts Below	PPV ≥3A(2R) ± SE
97.9% ± 0.0%	100.0%	—	39	**98.3%** ± 0.0%	97.7%	—
97.9% ± 0.0%	100.0%	—	38	**98.2%** ± 0.0%	96.5%	—
98.1% ± 0.2%	97.8%	**9.5%** ± 21.1%	37	**98.4%** ± 0.2%	91.7%	—
98.1% ± 0.2%	97.3%	**7.6%** ± 13.8%	36	**98.7%** ± 0.3%	90.2%	**5.4%** ± 3.2%
98.1% ± 0.2%	94.5%	**5.7%** ± 4.8%	35	**98.7%** ± 0.4%	84.1%	**4.0%** ± 2.2%
98.2% ± 0.3%	91.7%	**5.0%** ± 3.5%	34	**98.9%** ± 0.4%	79.1%	**4.1%** ± 1.7%
98.1% ± 0.3%	89.4%	**4.0%** ± 2.7%	33	**99.1%** ± 0.4%	72.4%	**3.8%** ± 1.3%
98.0% ± 0.3%	85.6%	**2.9%** ± 2.0%	32	**99.0%** ± 0.5%	63.1%	**2.9%** ± 0.9%
98.2% ± 0.4%	81.0%	**3.3%** ± 1.6%	31	**98.8%** ± 0.6%	54.1%	**2.3%** ± 0.7%
98.6% ± 0.4%	77.2%	**4.6%** ± 1.6%	30	**98.7%** ± 0.6%	50.6%	**2.1%** ± 0.6%
98.6% ± 0.4%	73.7%	**4.0%** ± 1.3%	29	**99.0%** ± 0.7%	40.8%	**2.1%** ± 0.5%
98.5% ± 0.5%	68.3%	**3.3%** ± 1.1%	28	**98.9%** ± 0.7%	39.1%	**2.1%** ± 0.5%
98.7% ± 0.5%	63.6%	**3.4%** ± 1.0%	27	**98.7%** ± 0.9%	31.6%	**1.9%** ± 0.4%
99.0% ± 0.5%	61.4%	**3.8%** ± 0.9%	26	**100.0%** ± 0.0%	26.8%	**2.3%** ± 0.1%
99.3% ± 0.5%	56.0%	**3.8%** ± 0.7%	25	**100.0%** ± 0.0%	22.1%	**2.2%** ± 0.1%
99.1% ± 0.6%	47.5%	**3.2%** ± 0.6%	24	**100.0%** ± 0.0%	18.4%	**2.1%** ± 0.1%
99.0% ± 0.6%	41.8%	**2.9%** ± 0.5%	23	**100.0%** ± 0.0%	14.1%	**2.0%** ± 0.1%
98.9% ± 0.7%	38.8%	**2.7%** ± 0.5%	22	**100.0%** ± 0.0%	11.0%	**1.9%** ± 0.1%
98.8% ± 0.8%	33.6%	**2.5%** ± 0.4%	21	**100.0%** ± 0.0%	9.8%	**1.9%** ± 0.1%
100.0% ± 0.0%	24.3%	**2.8%** ± 0.2%	20	**100.0%** ± 0.0%	8.1%	**1.8%** ± 0.1%
100.0% ± 0.0%	<22.4%	**≤2.7%** ± 0.1%	≤19	**100.0%** ± 0.0%	≤5.4%	**≤1.8%** ± 0.0%

Lower probability of ACR

Elevated immune monitoring early after cardiac transplantation is associated with increased plaque progression by intravascular ultrasound

Clin Transplant 2015: 29: 103–109 DOI: 10.1111/ctr.12489

	Group 1 IM assay score <406 ng ATP/mL, n = 38	Group 2 IM assay score ≥406 ng ATP/mL, n = 12	p-value
Recipient age (yr)[a]	55.9 ± 11.7	51.7 ± 15.6	0.403
Recipient female gender (%)[a]	10/38 (26.3)	4/12 (33.3)	0.718
Mean IM assay score (ng ATP/mL)	176.4 ± 102.2	616.3 ± 239.5	N/A
Time after transplant (days)			
Baseline IVUS	47.3 ± 16.1	44.7 ± 12.7	0.561
1-yr IVUS	369.9 ± 25.6	379.8 ± 18.7	0.158
Segment length (mm)			
Baseline IVUS	35.2 ± 5.1	36.4 ± 5.8	0.529
1-yr IVUS	35.2 ± 5.1	36.4 ± 5.8	0.528
Total ischemic time (min)[a]	206.1 ± 53.7	215.4 ± 39.3	0.671
CMV mismatch (%)[a]	17/35 (48.6)	2/11 (18.2)	0.092
Induction with ATG (%)[a]	14/37 (37.8)	3/11 (27.3)	0.723
Prednisone daily dosage (mg)	14.7 ± 3.0	15.8 ± 1.0	0.043
Tacrolimus level (ng/mL)	10.4 ± 3.7	10.1 ± 4.7	0.860
Tacrolimus at six months (%)[a]	35/38 (92.1)	12/12 (100.0)	1.000
mTOR at six months (%)[a]	4/38 (10.5)	0/12 (0)	0.560
Ischemic etiology (%)[a]	12/38 (31.6)	6/12 (50.0)	0.309
2R/3R rejection in first yr (%)[a]	3/38 (7.9)	0/12 (0)	1.000
Pre-transplant PRA ≥10%[a]	13/37 (35.1)	3/11 (27.3)	0.729
Donor-specific antibodies[a]	5/37 (13.5)	1/10 (10)	1.000
HLA mismatch (%)[a]			
0	3/35 (8.6)	2/10 (20.0)	0.538
1	13/35 (37.1)	4/10 (40.0)	
2	19/35 (54.3)	4/10 (40.0)	
Rapid progression of MIT ≥0.5 mm (%)	5/38 (13.2)	10/12 (83.3)	N/A
Δ MIT (mm)	0.3 ± 0.2	0.7 ± 0.4	0.004
Δ MIA (mm^2/yr)	1.4 ± 1.3	4.0 ± 3.7	0.032
Δ average percent stenosis (%/yr)	4.4 ± 3.9	13.5 ± 10.0	0.009
Δ plaque volume per 1 mm (mm^3/mm/yr)	0.7 ± 0.9	2.1 ± 1.8	0.024
Risk ratio for developing rapid progression of MIT ≥0.5 mm (95% confidence interval)	–	11.7 (2.9–47.0)	<0.001

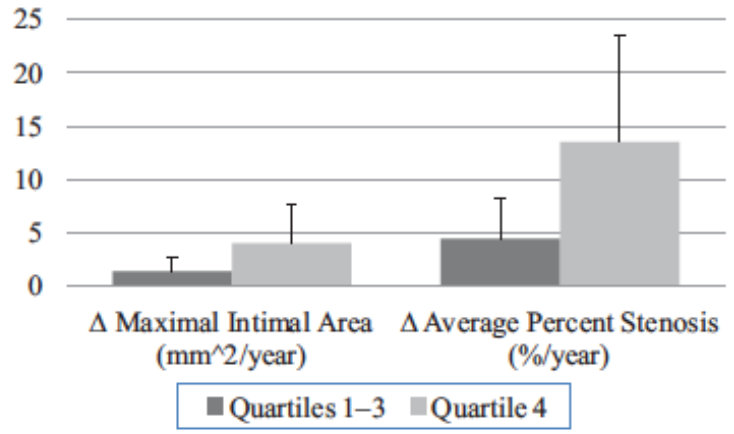
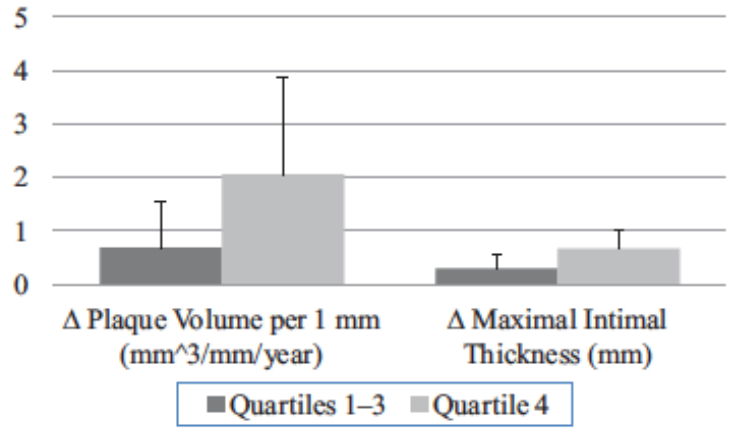


Fig. 1. Intravascular ultrasound outcomes by quartiles of early two-month immune monitoring assay scores: maximal intimal area and average percent stenosis.



Everolimus use and CMV mismatch more frequent in group 1 !!

IMAGE TRIAL

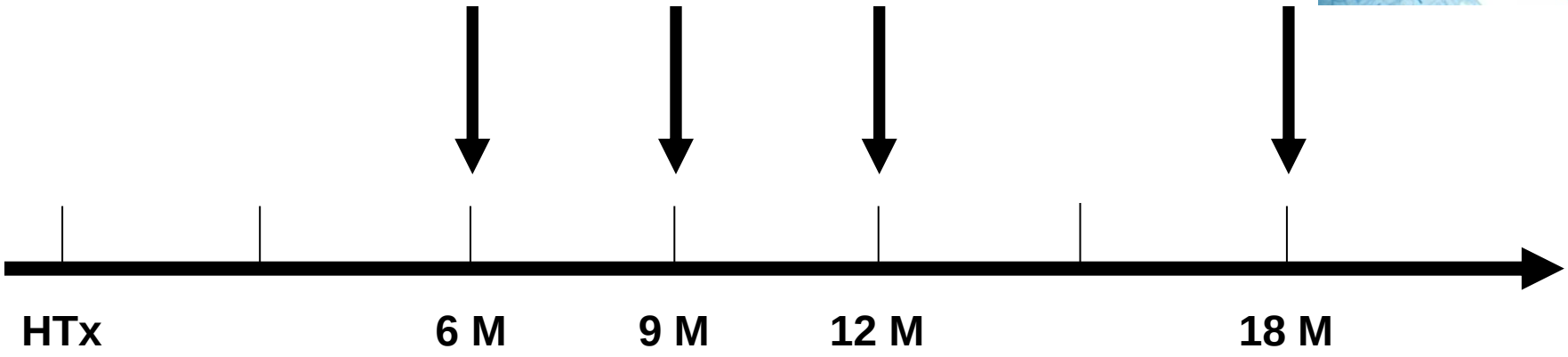
- **Is rejection monitoring primarily based on AlloMap® safe?**
- **Clinical outcome in both groups was the same, with a similar 2-year survival period.**
- **Patients in the AlloMap® group were subjected to considerably fewer EMBs.**
- **This study shows not only that monitoring rejection using AlloMap® is safe, but also that it reduces the EMB-associated risks cuts costs and can increase the quality of life of the patient** *(Pham et al. 2010)*

CARGO II

- **499 patients confirmed the results of the initial CARGO study similarly revealing a high negative predictive value (95.5%) for graft rejection in patients >6 months after HTx** *(Crespo-Leiro et al. 2016)*

- **A recent analysis of 737 patients from the CARGO II trial suggested that the intra-individual AlloMap® score variability may be useful to predict the future course after HTx** *(Crespo-Leiro et al. 2015)*

METHODS – Time points of AlloMap® scoring



1. Predictive value of AlloMap score at each time point

2. Predictive value of dynamic changes

HTx between 02/2006 – 11/2007

AlloMap® score available at 6, 9, 12 and 18 months post HTx: n=57 pts.

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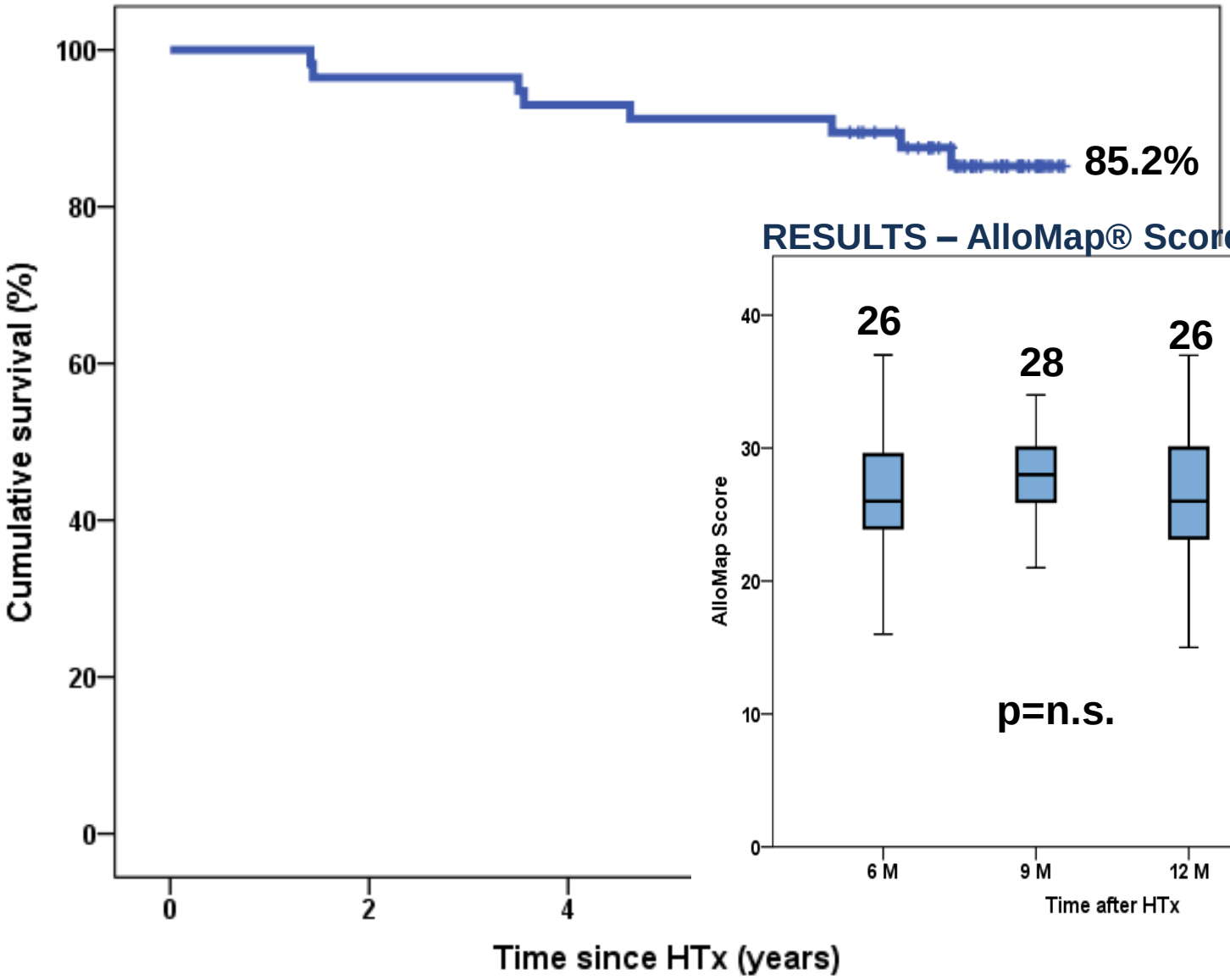
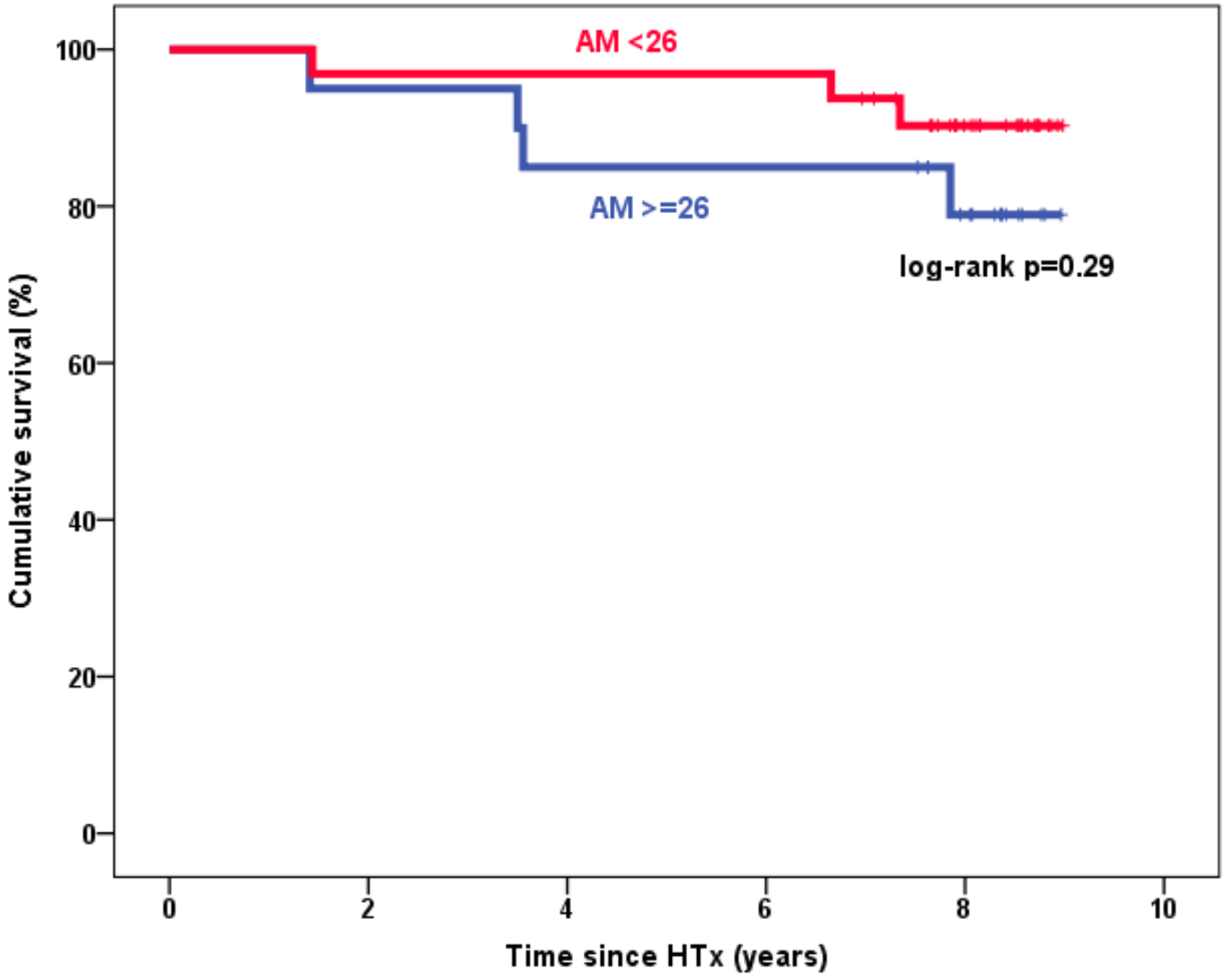
Predictive Value of Gene Expression Profiling as Assessed By AlloMap® Score for Long-Term Survival After Heart Transplantation
B. Fujita , E. Prashovikj, U. Schulz, J. Sunavsky, U. Fuchs, J. Börgermann, J. Gummert, S. Ensminger
The Journal of Heart and Lung Transplantation, Vol 34, No 4S, April 2015

RESULTS – Overall survival

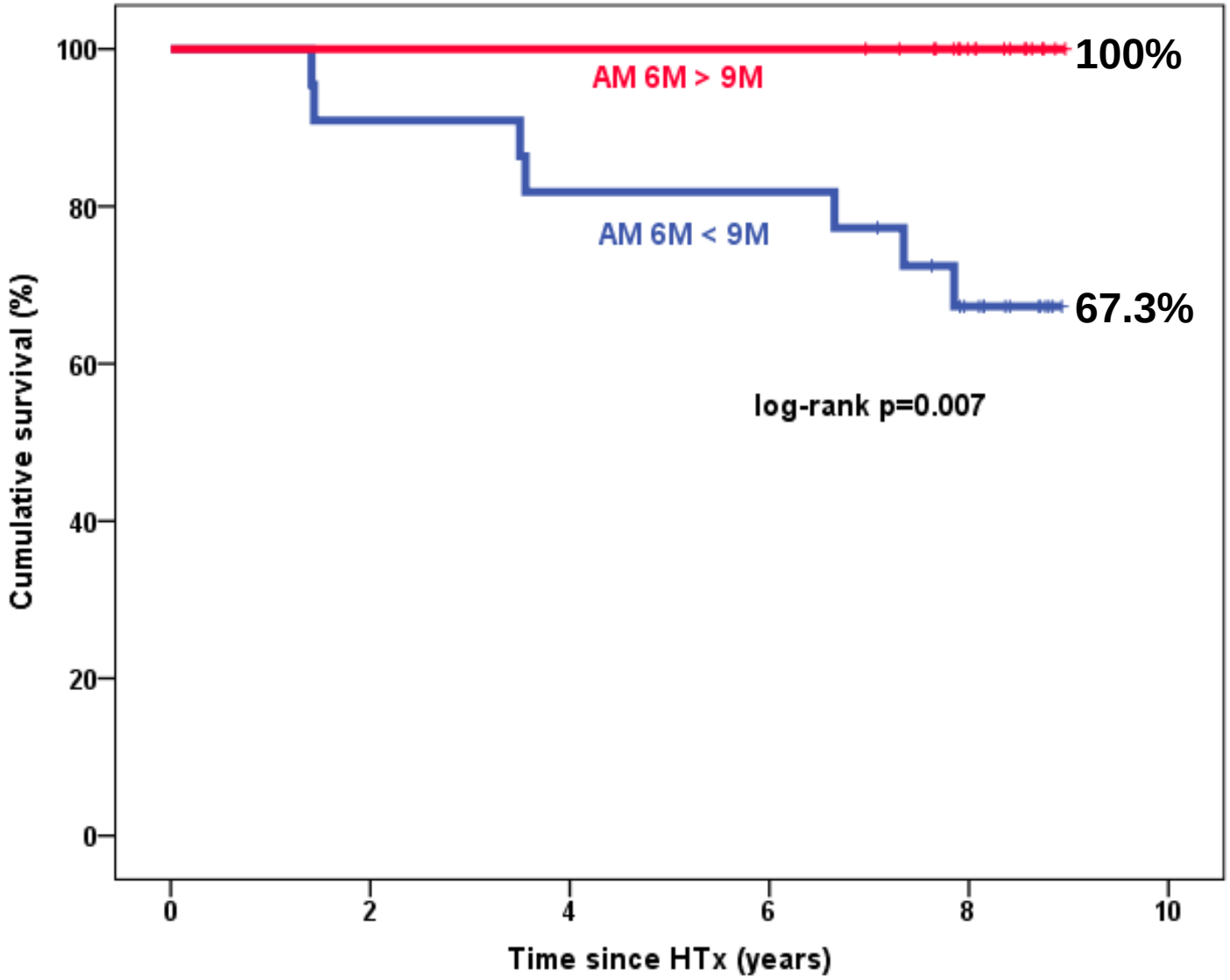


RESULTS – AlloMap® Score distribution

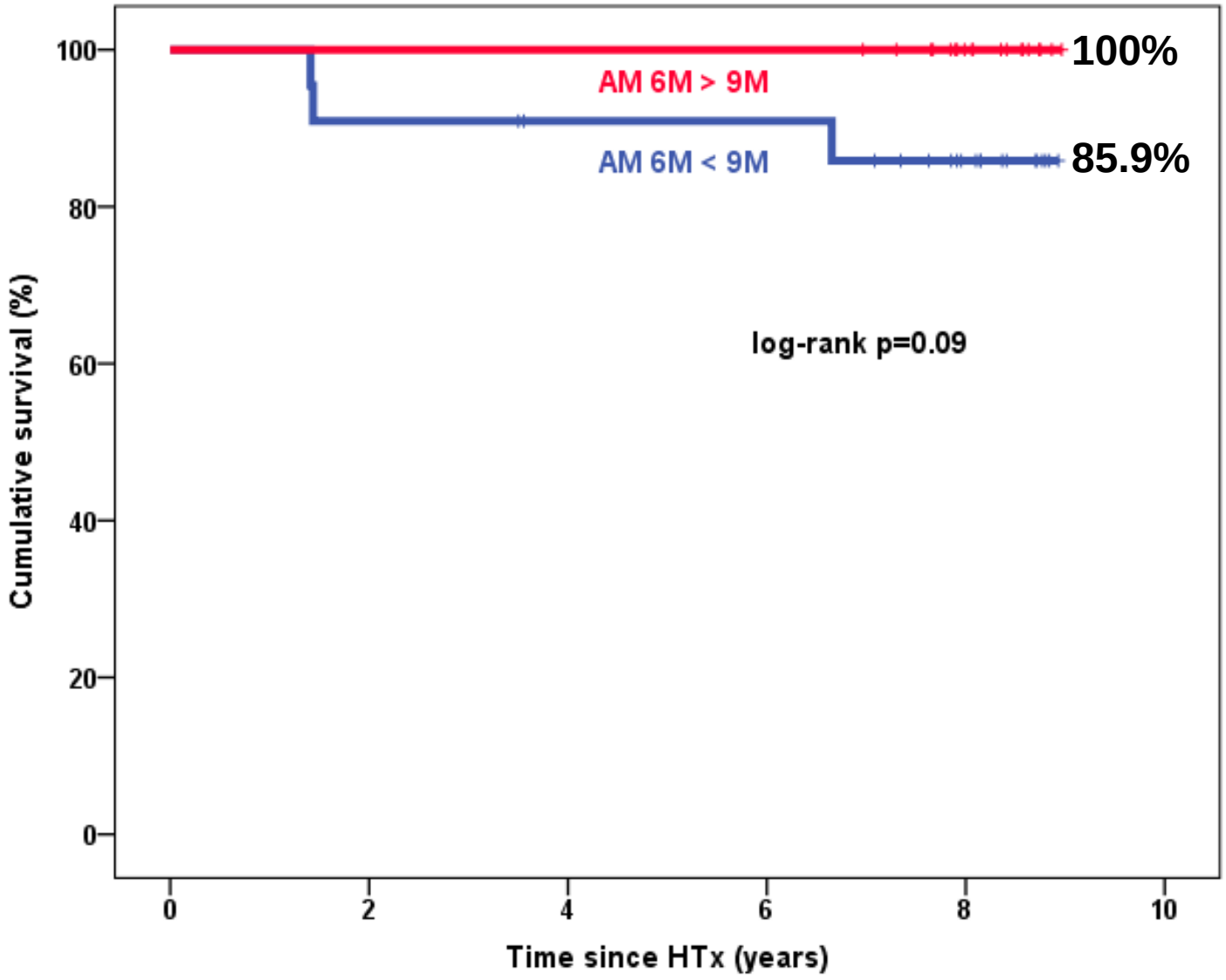
RESULTS – Predictive value of AlloMap at 6 months after HTx



An increase in AlloMap from 6 to 9 months increases risk for death – overall survival



An increase in AlloMap from 6 to 9 months increases risk for death – rejection free survival



Peripheral biomarkers for individualizing immunosuppression in transplantation - Regulatory T cells

Stephan Schlickeiser [a], Birgit Sawitzki [a,b,*]

Indication	Organ	Analyzed parameter	Outcome	Ref.
Pre-transplant	Kidney	$CD4^+CD25^+CD127^{low}Foxp3^+$	Increased co-expression of Foxp3 in $CD25^+CD127^{low}$ cells in rejection-free patients	[91]
		$CD4^+CD25^+Foxp3^+$	Increased frequency in patients developing acute rejection	[92]
Immuno-suppression/ conversion	Kidney	$CD4^+CD25^+Foxp3^+$	Increased ratio between memory T cells and Tregs in rejecting patients upon Tac withdrawal	[100]
		$CD4^+CD25^{high}$	Increased reconstitution when combining Thymo with sirolimus in comparison to CsA	[93]
		$CD4^+CD25^+Foxp3^+$	Increased frequency upon Campath-1H induction	[101]
		$CD4^+CD25^{high}$	Increased reconstitution when combining Campath-1H with sirolimus in comparison to CsA but no protection from chronic rejection	[94]
		$CD4^+CD25^+Foxp3^+$	Increased frequency and suppressive function in patients receiving rATG/Bela/SRL	[96]
		$CD4^+CD25^+Foxp3^+$	Transient but no long term loss of belatacept/basiliximab combination	[107]
		$CD4^+CD25^+Foxp3^+$	No decrease in frequency and function upon basiliximab induction	[110]
		$CD4^+CD25^+CD127^{low}Foxp3^+$	Loss of $CD25^+Foxp3^+$ cells but no functional defect upon basiliximab induction	[108]
		$CD4^+CD25^+Foxp3^+$	Drop in frequency after transplantation in patients on CNI and no recovery until 12 months	[124]
		$CD4^+CD25^+Foxp3^+$	Recovery 2 years after transplantation, negative correlation with Tac levels	[98]
		$CD4^+CD25^+CD127^{low}$	Increased frequency at 3 months after conversion to mTOR inhibitors	[95]
	Liver	$CD4^+CD25^+Foxp3^+$	Increase in frequency upon CNI to MMF conversion	[99]
		$CD4^+CD25^+Foxp3^+$	Maintenance of $Foxp3^+$ T cells following basiliximab induction	[109]
Graft function/rejection	Kidney	$CD8^+CD28^-Foxp3^+$	Decreased frequency during acute rejection	[111]
		$CD4^+CD25^+Foxp3^+$	Decreased frequency during acute rejection	[92]
		$CD4^+CD25^+CD127^{low}Foxp3^+$	No correlation with graft function when comparing patients with stable function and those with CAN	[112]
		Foxp3 mRNA	No difference between stable and CR patients	[113]
	Liver	$CD8^+CD28^-$	Expansion in adult to adult living donor liver recipients + association with reduced incidence of acute and chronic rejection	[115]
		$CD4^+CD25^{high}Foxp3^+$	Decrease in peripheral frequency during acute rejection in pediatric liver recipients	[114]
Operational tolerance	Kidney	$CD4^+CD25^{high/int}$	Decreased frequency of $CD4^+CD25^{int}$ effector T cells in tolerant compared to CR patients	[116]
		Ratio of Foxp3/aMann mRNA	Increased in tolerant patients in comparison to stable and CR patients	[116]
		$CD4^+CD25^+Foxp3^+$	Increased levels as compared to CR and stable patients	[117]
	Liver	$CD4^+CD25^+Foxp3^+$	Increased frequency in tolerant versus IS-dependent patients	[118]
		Foxp3 mRNA	3.5 Fold increase in successfully weaned patients	[125]
		$CD4^+CD25^+Foxp3^+CD45RA^{+/-}$	Increased frequency of conv. ($CD45RA^-$) Tregs in tolerant and decreased frequency of naïve ($CD45RA^+$) Tregs in intolerant pediatric patients	[119]

Peripheral biomarkers for individualizing immunosuppression in transplantation - Regulatory T cells

Stephan Schlickeiser [a], Birgit Sawitzki [a,b,*]

- Identify „high-risk“ and „operational tolerant“patients
- Less effective in association with graft function and occurrence of chronic rejection

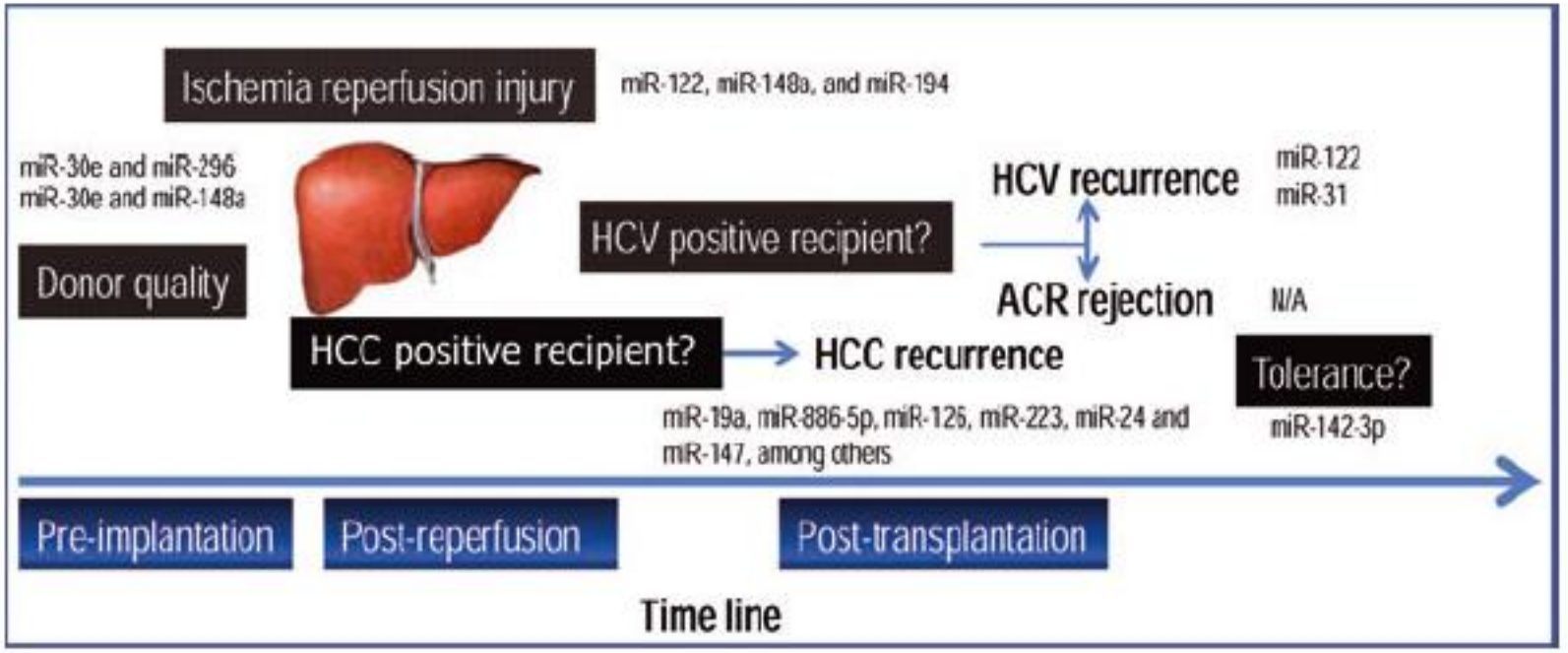
Table 1
Markers of human peripheral blood natural regulatory T-cells.

	Marker	Reference
Cell surface	High CD25	[120]
	Low CD127	[64]
	CD45RA/RO	[8]
	CTLA-4	[11,121]
	GITR	[122]
	CD95	[14]
	ICOS	[63]
	HLA-DR	[63]
	GARP	[67,68]
	LAG-3	[10]
	CD39/73	[19]
	Galectin-3	[123]
Intracellular	Foxp3	[58]
	Helios	[65]
	Demethylated TSDR	[73,75]

MicroRNAs as Biomarkers in Solid Organ Transplantation

V. R. Mas[a,*], C. I. Dumur[b], M. J. Scian[a], R. C. Gehrau[a] and D. G. Maluf[a]

American Journal of Transplantation 2013; 13: 11–19



MicroRNAs as Biomarkers in Solid Organ Transplantation

V. R. Mas[a,*], C. I. Dumur[b], M. J. Scian[a], R. C. Gehrau[a] and D. G. Maluf[a]

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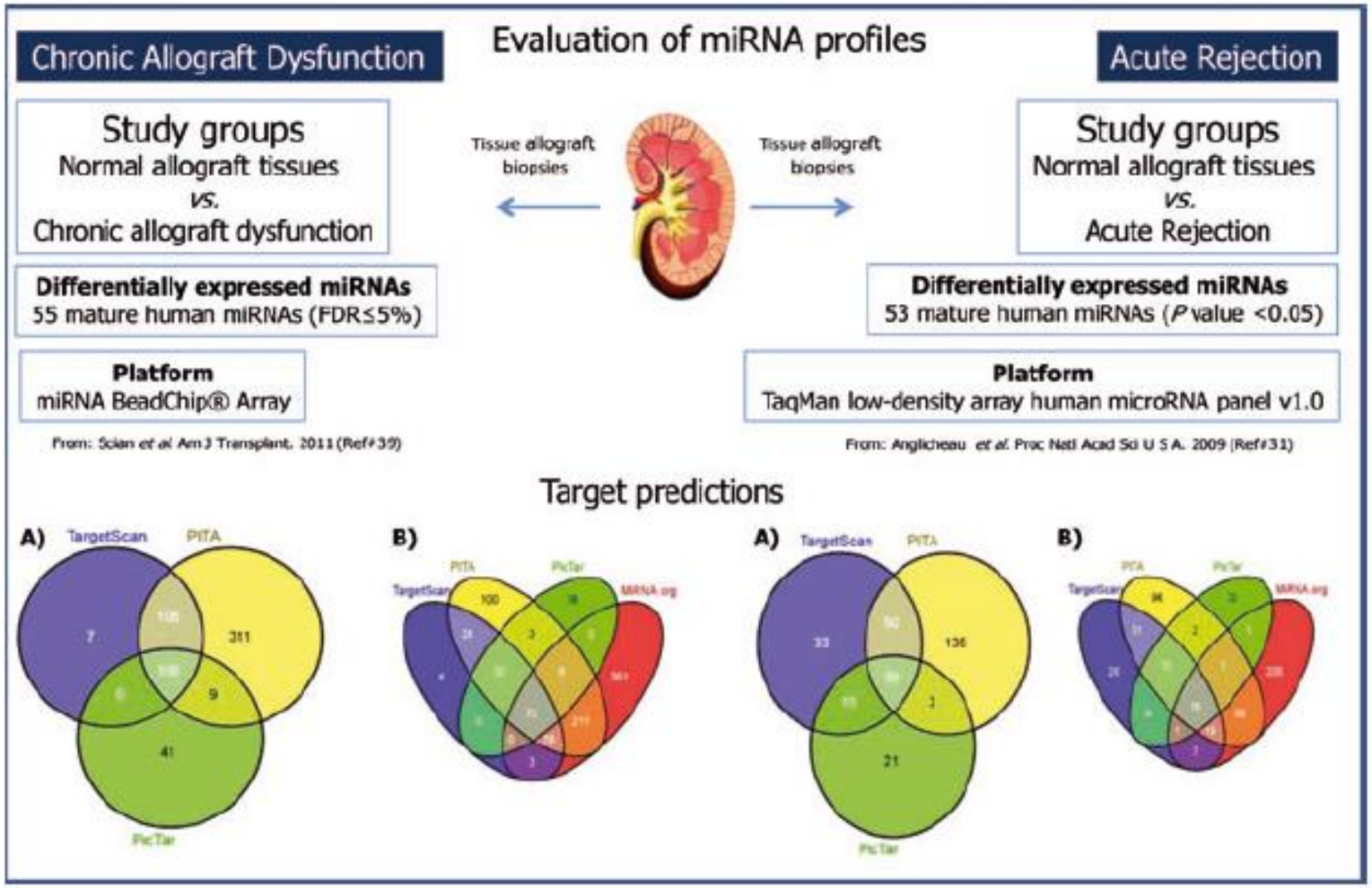

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MicroRNAs as Biomarkers in Solid Organ Transplantation

V. R. Mas[a,*], C. I. Dumur[b], M. J. Scian[a], R. C. Gehrau[a] and D. G. Maluf[a]

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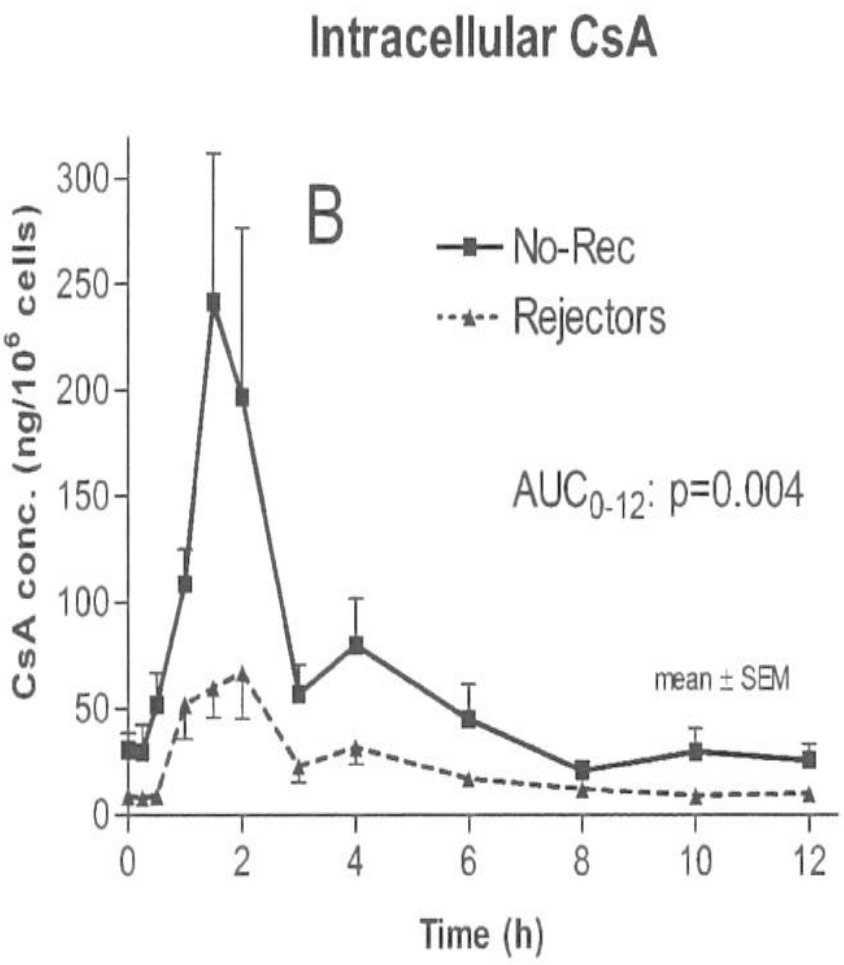
Major challenges miRNAs in solid organ transplantation

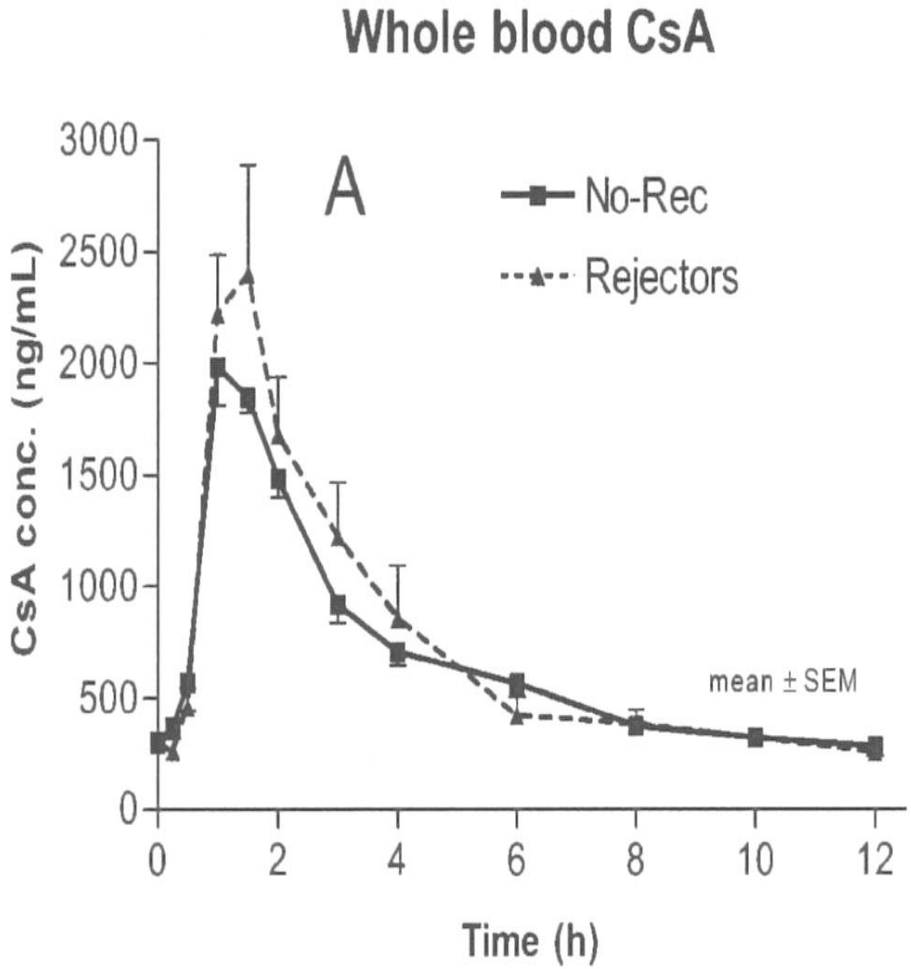
(1) yet many unanswered questions regarding miRNA biology
(2) the mechanism of regulation of miRNA production is not completely clear
(3) many miRNAs are located within introns of host genes,
their expression does not always correlate perfectly with
that of host genes suggesting further, posttranscriptional,
regulation
(4) specific targets for most miRNAs remain unclear

Positive points

miRNAs have the potential of being reliable biomarkers because they are tissue specific, stable in different biological fluidics (including archival samples), relate with clinical conditions and can be measured using cost-effective technology

Intracellular CsA T-lymphocyte concentration has a potential of predicting rejection





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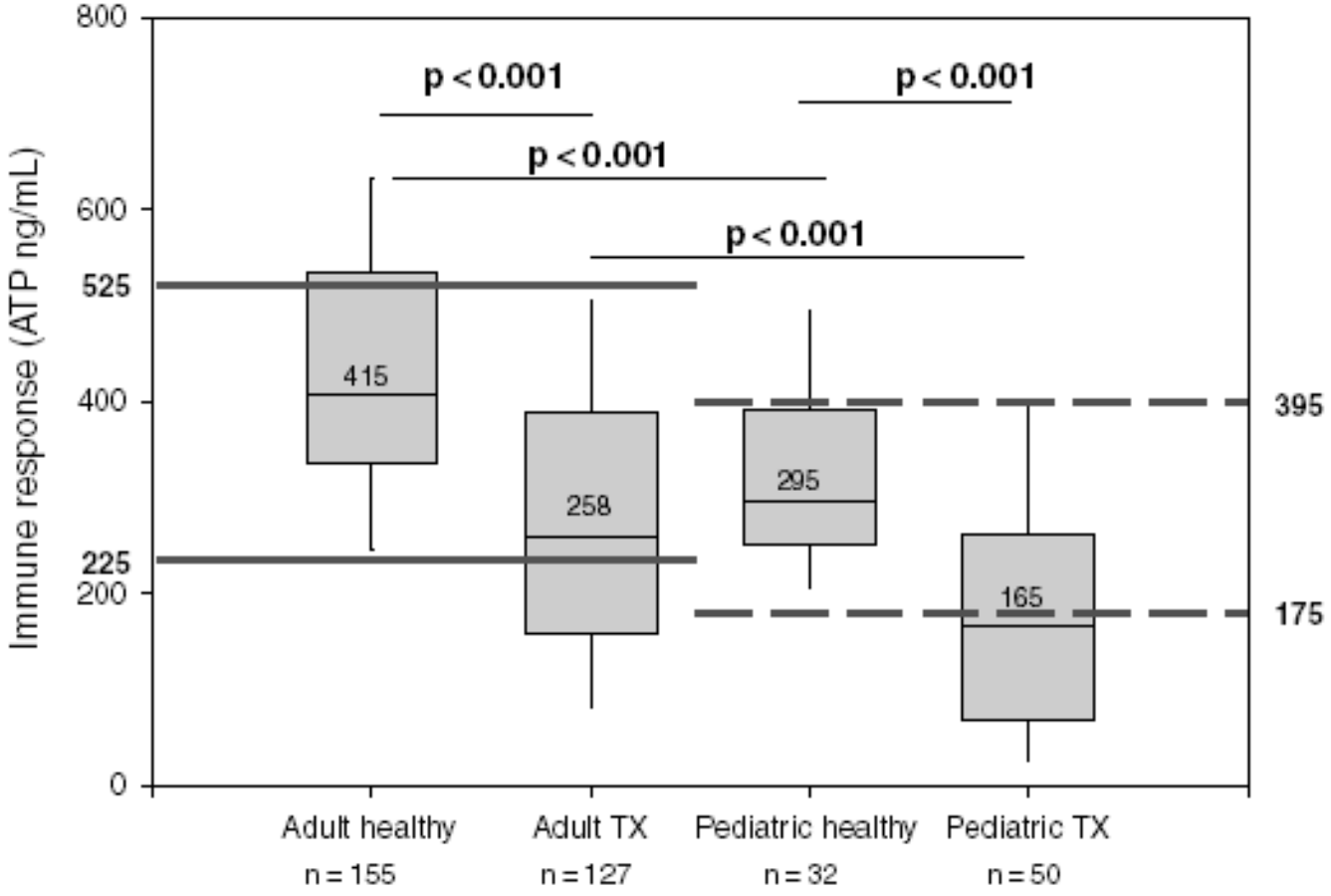
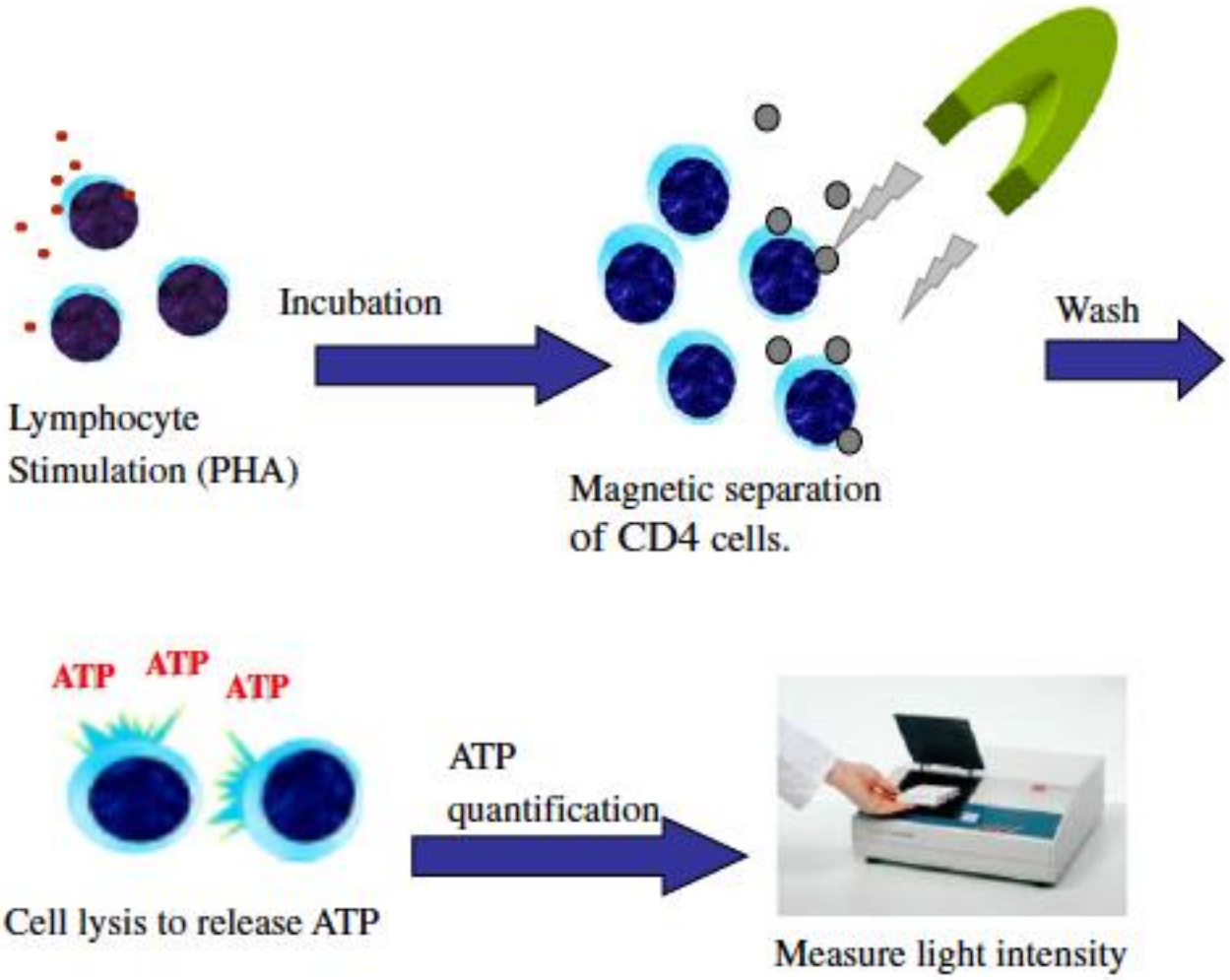
Falck et al, Transplantation 2008;85:179-184

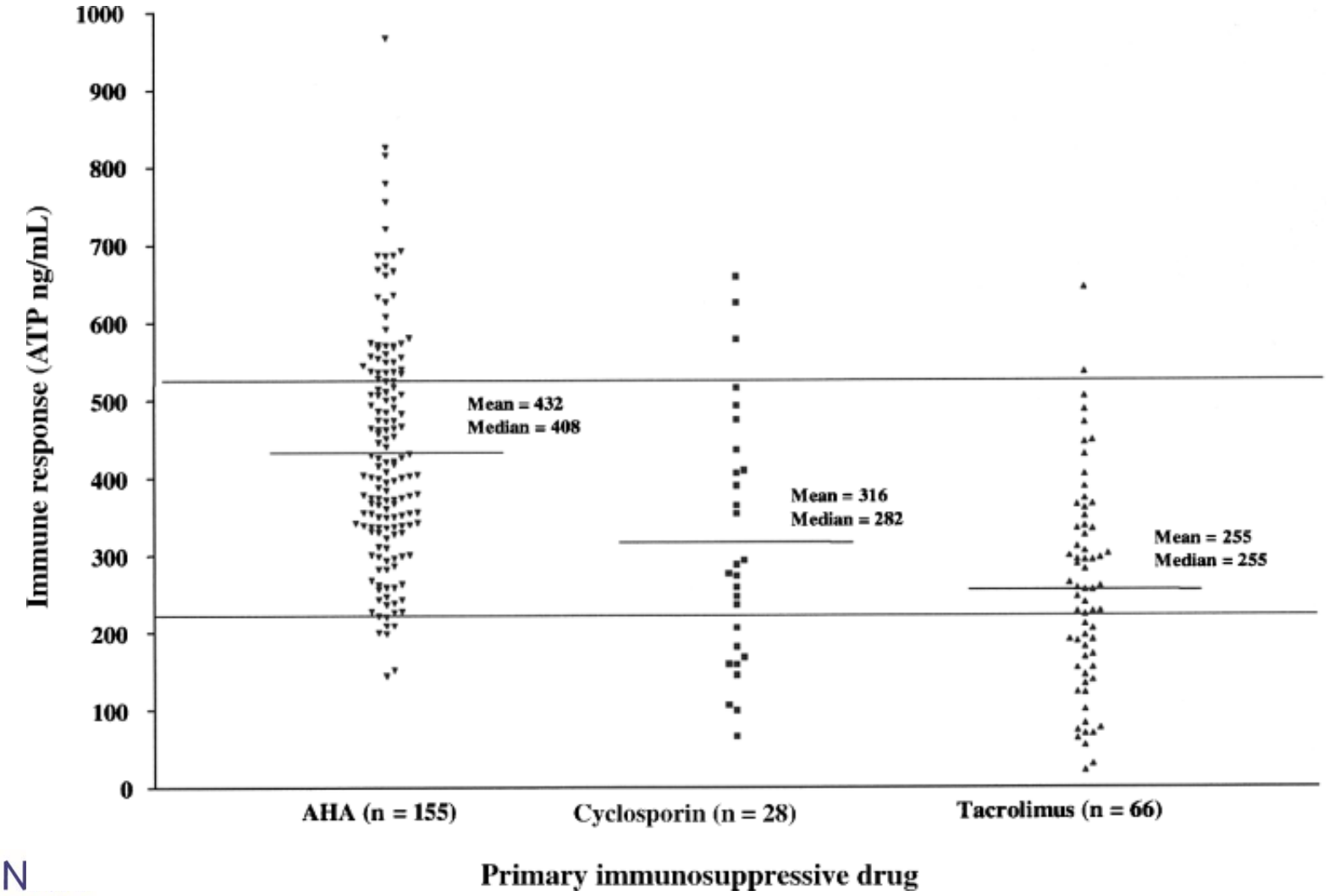
Immune response (Cylex™) distributions for healthy/transplant adults and healthy/transplant children < 12 yr



Hooper et al, Clin Transplant. 2005; 19:834-839


Incubation
Wash
Lymphocyte
Stimulation (PHA)
Magnetic separation
of CD4 cells.
ATP
ATP
ATP
ATP
quantification
Cell lysis to release ATP
Measure light intensity

Comparison of Cylex™ immune cell response between patients receiving different calcineurin inhibitors



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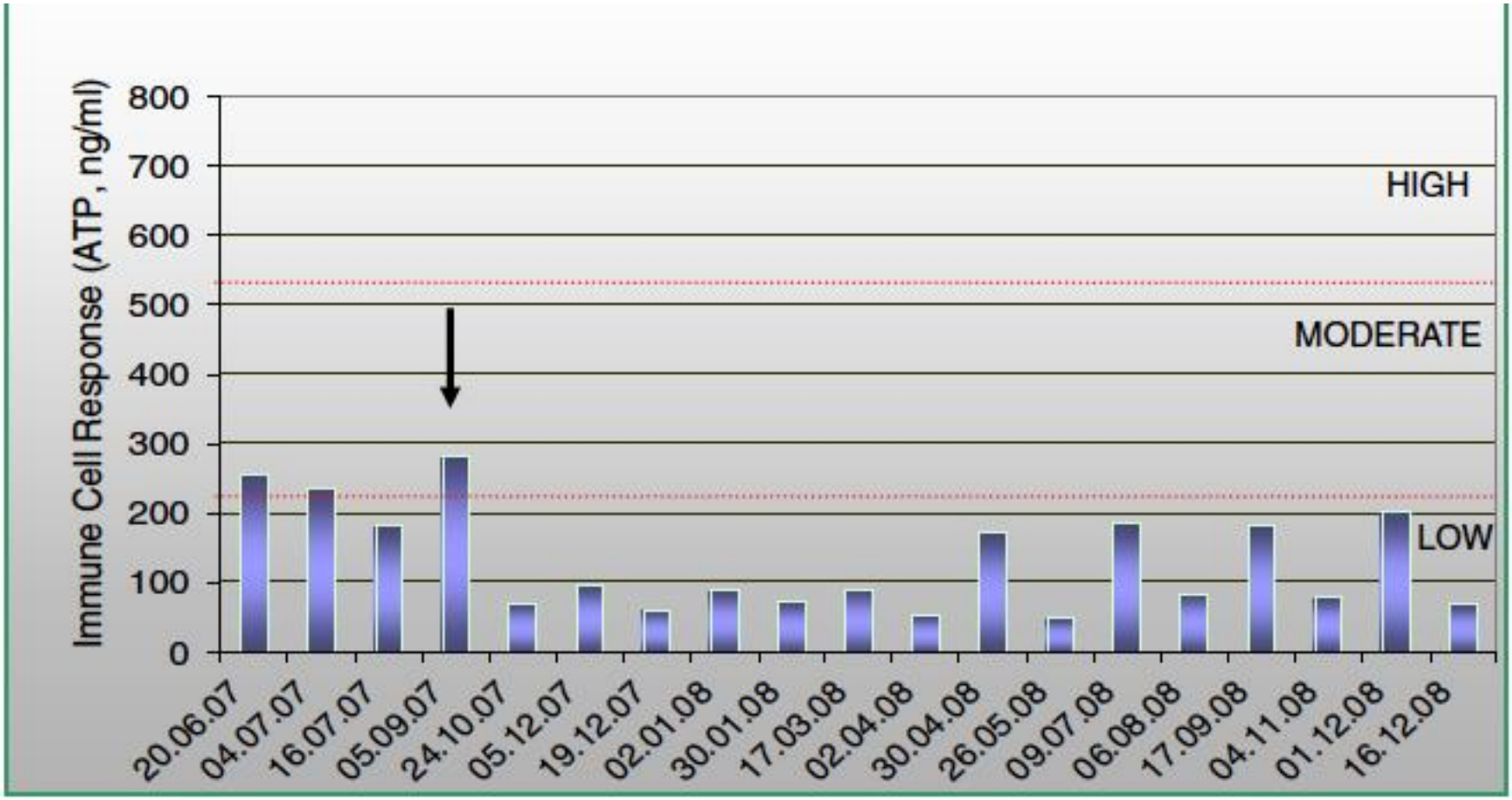
Kowalski et al, Clin Transplant. 2003;17:77-88

Confronting the challenge: Individualized immune monitoring after organ transplantation using the cellular immune function assay

Moshe Israeli [a,*], Tirza Klein [a], Gunnar Brandhorst [b], Michael Oellerich [b]



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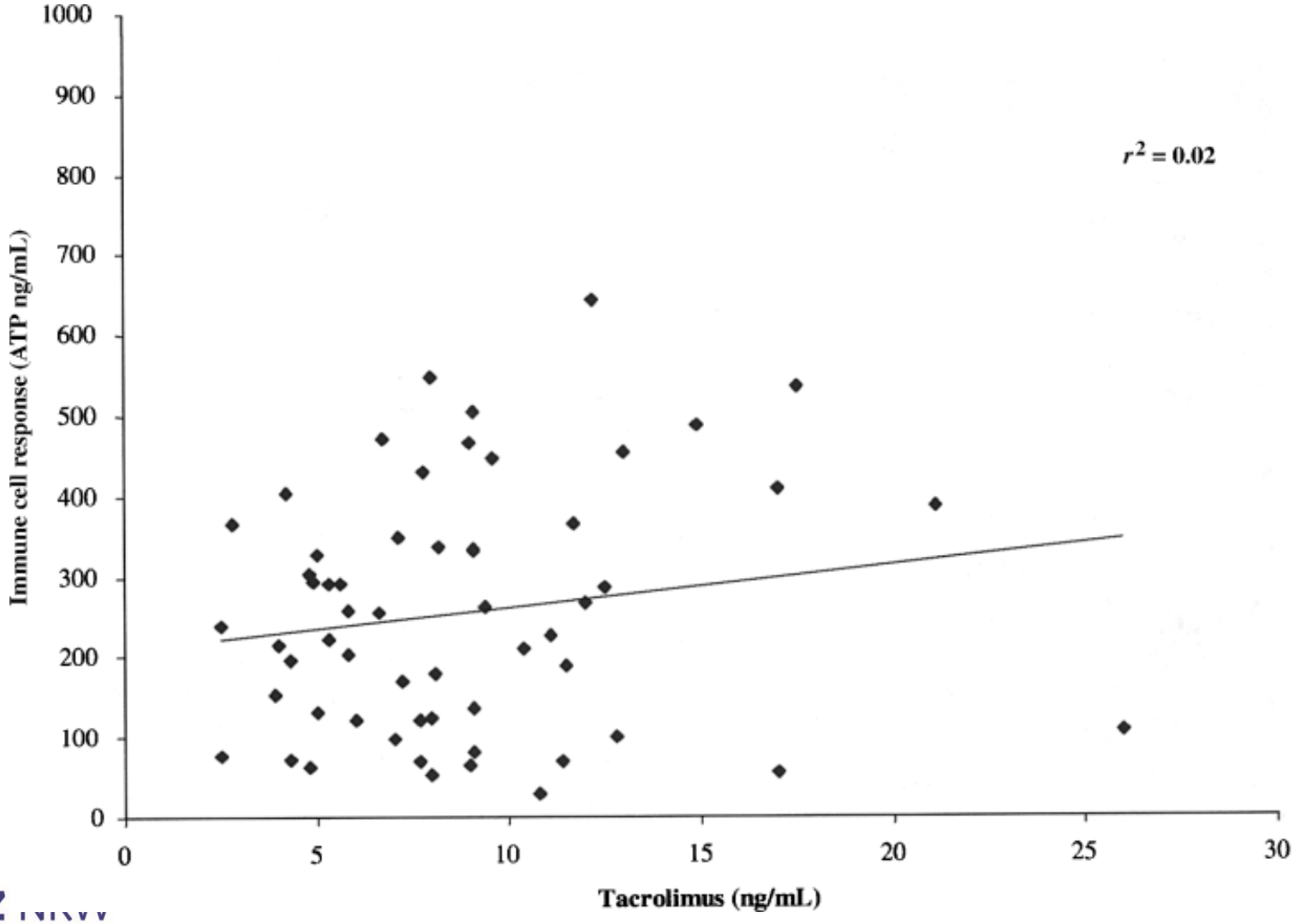
Lack of correlation between immune cell response and tacrolimus (TDM) levels



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Kowalski et al, Clin Transplant. 2003; 17:77-88

Update on Immune Monitoring in Heart Transplantation

Curr Transpl Rep (2015) 2:329–337

M. G. Crespo-Leiro[1,2] · E. Barge-Caballero[1,2] · M. J. Paniagua-Martin[1,2] · G. Barge-Caballero[1] · N. Suarez-Fuentetaja[2]

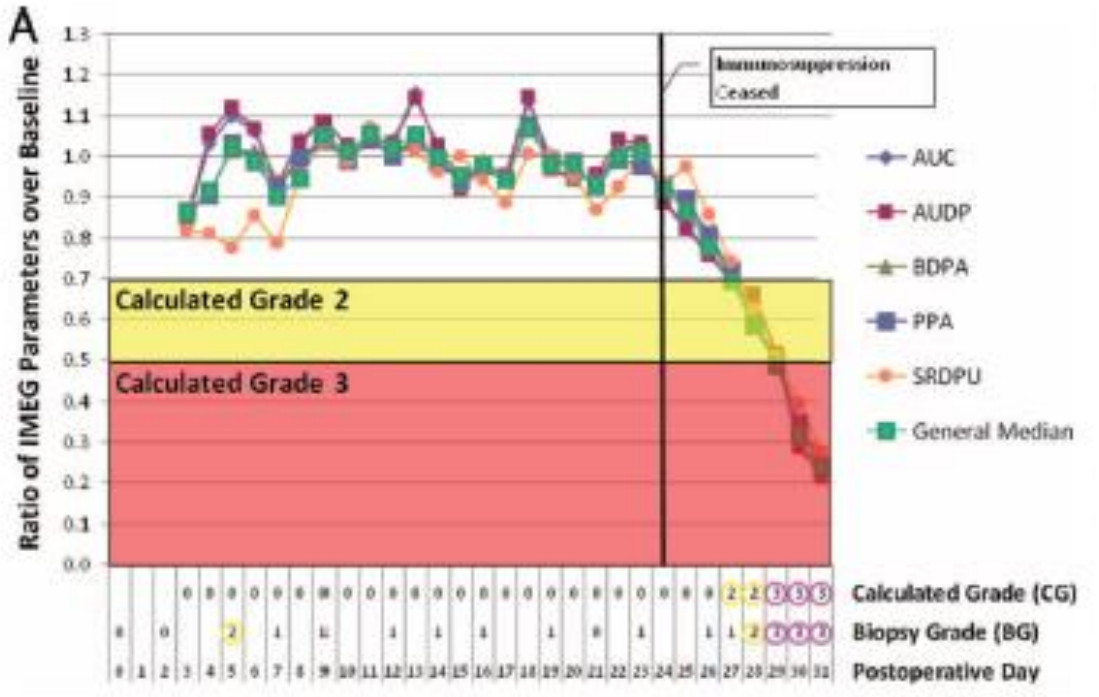
Table 1 Immune monitoring tools that have been investigated in heart transplant recipients

Immune monitoring assays	Comments
AlloMap® gene expression profiling test (CareDx, Brisbane, USA)	Genomic marker of rejection 20-gene algorithm based on the gene expression profile of 11 genes associated with acute cellular rejection and 9 genes used for normalization and quality control AlloMap test score (0–40) Sensitive marker for moderate or higher cellular rejection. Low specificity. Not validated for AMR.
ImmuKnow® assay (Cylex Inc, Columbia, MD, USA)	T functional assay Marker of T cell activation Measures ATP release from activated CD4+ T lymphocytes Defines three immunological responses zones: Low ≤225 ng/mL Moderate 226–254 ng/mL High ≥525 ng/mL Usefulness in HT is not well known
ELISPOT	T functional assay Marker of cytokine-producing T cells Usefulness in HT is not well known
Antibody monitoring	Solid-phase and/or cell-based assays to assess for DSA and quantification of antibodies. The presence of anti-HLA DSA antibodies has been associated with allograft injury, cellular rejection, AMR, CAV and poor survival. Anti-HLA monitoring is recommended after HT and if AMR is suspected Non-HLA antibody monitoring may be considered when anti-HLA antibodies are absent and AMR is suspected
Donor-derived cell-free DNA	Correlates with cardiac rejection Under investigation
Micro-RNA	Correlates with cardiac rejection Under investigation

AMR antibody-mediated rejection, *DSA* donor-specific antibodies

Novel Implantable Device to Detect Cardiac Allograft Rejection

Circulation September 15, 2009



Summary

- optimal combinations of biomarkers may be necessary
- baseline values for individual patients may be required
- no prospectively validated target ranges for adult and pediatric patients are available
- independent prospective clinical outcome studies are in progress
- development of "tolerance permissive" immunosuppressive regimens would be desirable
- FDA-approved tools are Immuknow/Cylex (iATP) and AlloMap/XDX (GEP)