28.11.2015 – 17. Transplantationsworkshop

Neue Therapieprinzipien in der Immunsuppression oder bewährte Standardtherapie nach Nierentransplantation - Wo stehen wir?

Bernhard Banas
Abteilung für Nephrologie

Immunsuppression nach Nierentransplantation in Deutschland

Immunsuppression initial

	2012		2011	
	n	%	n	%
Patient nimmt an randomisierter Doppelblindstudie teil				
Alle Patienten	N = 2.570		N = 2.832	
(1) ja	46	1,8	105	3,7
(0) nein	2.524	98,2	2.727	96,3
davon				
Induktionstherapie	2.019	78,6	1.988	70,2
davon				
ATG	447	22,1	516	26,0
OKT3	3	0,15	4	0,20
Il-2-Rezeptorantagonist	1.580	78,3	1.465	73,7
andere Antikörper	90	4,5	95	4,8
Cyclosporin	701	27,8	745	27,3
Tacrolimus	1.807	71,6	1.976	72,5
Azathioprin	11	0,44	11	0,40
Mycophenolat	2.406	95,3	2.596	95,2
Steroide	2.502	99,1	2.700	99,0
m-ToR-Inhibitor	41	1,6	71	2,6
andere	54	2,1	53	1,9

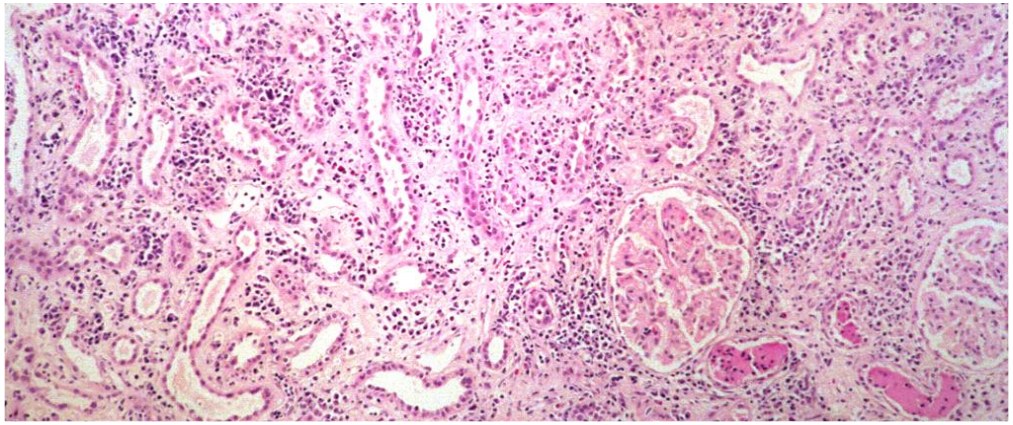
Frage des Tages

Ist es überhaupt noch notwendig die immunsuppressive Behandlung zu verbessern ?

Inzidenz der akuten Rejektion

Deutschland: AQUA-Daten 2014

	n	%
Alle Patienten	N = 2.137	
akute behandlungsbedürftige Rejektion Niere		
(0) nein	1.827	85,49
(1) ja	310	14,51

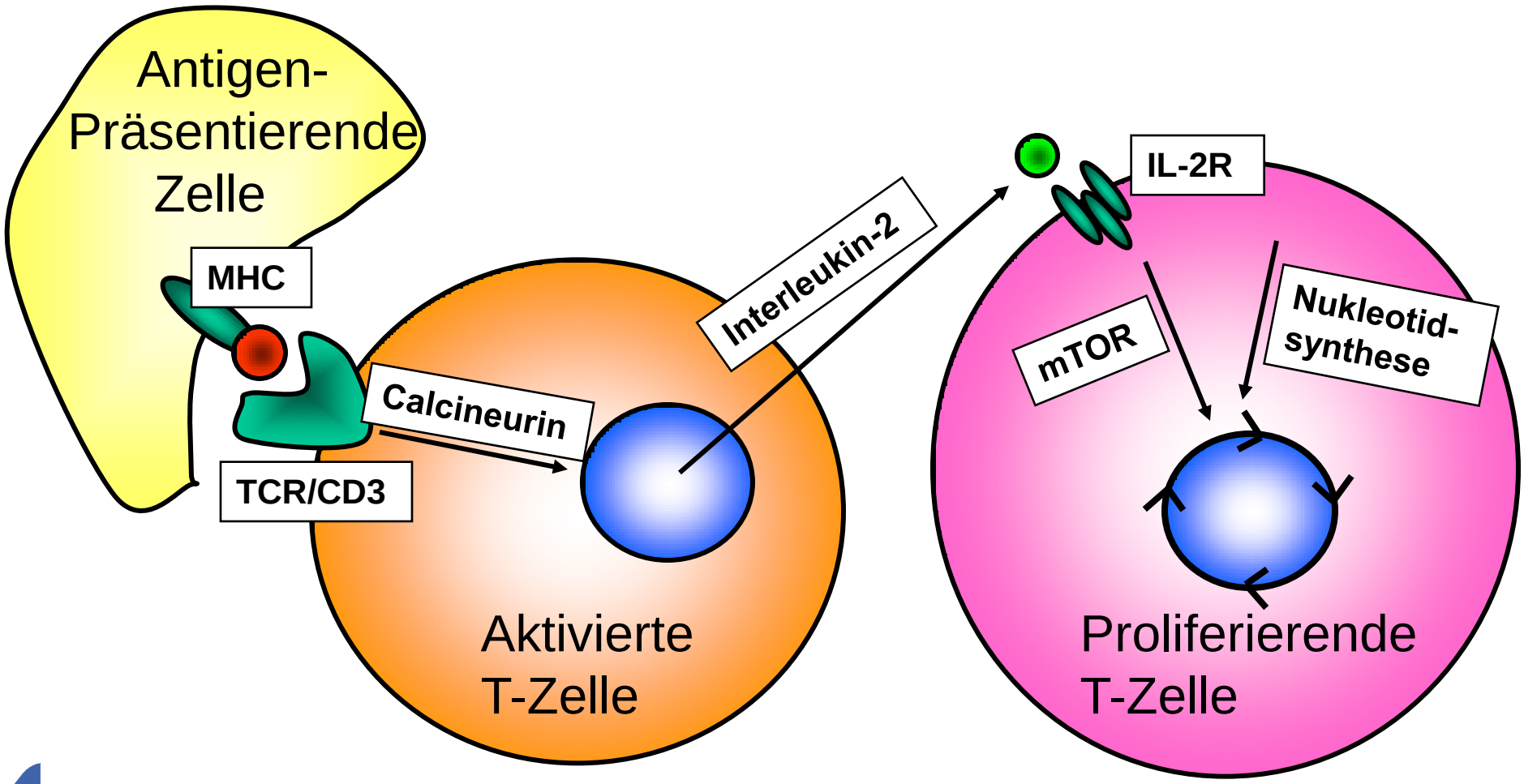


ZUKUNFT DURCH QUALITÄT

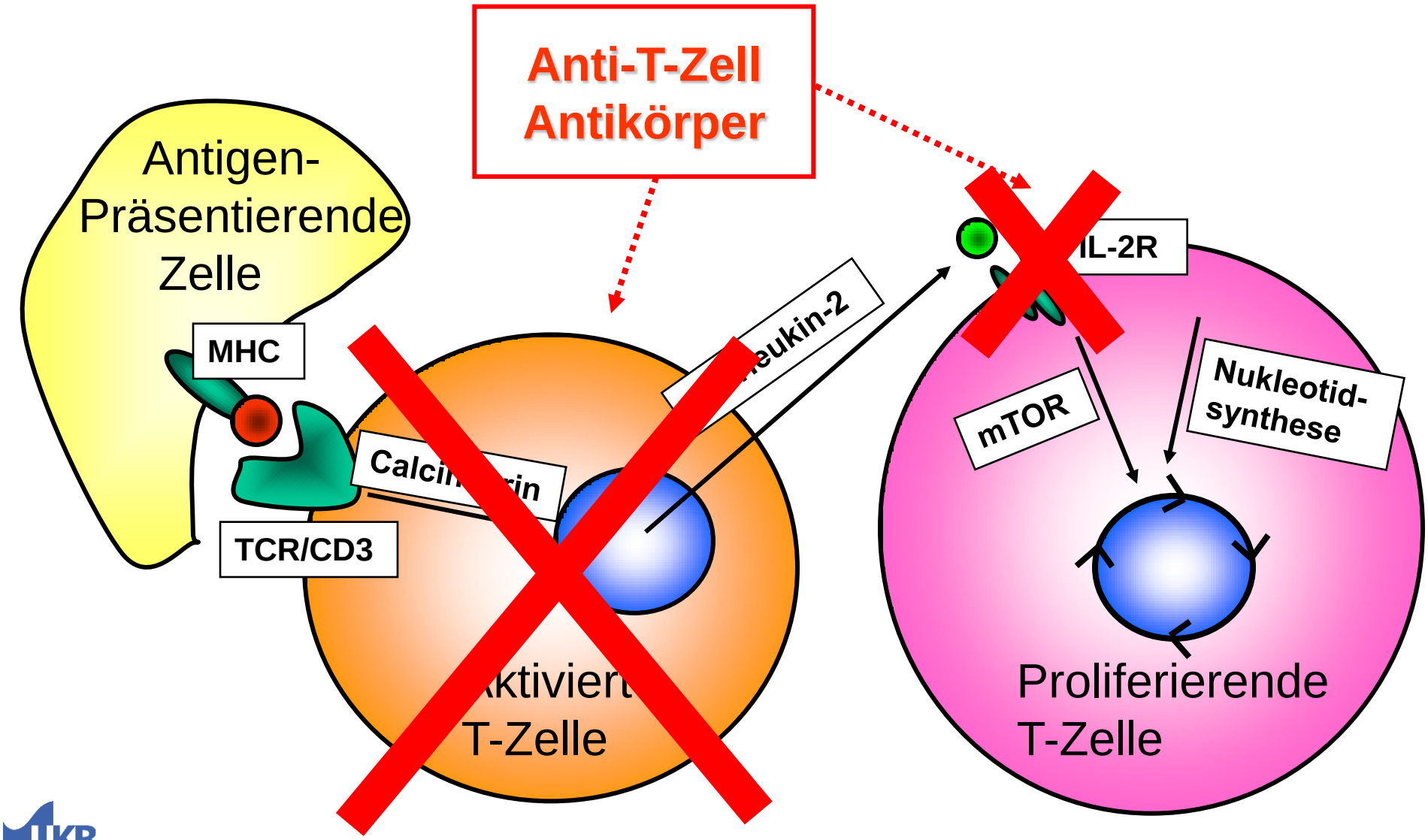
Outcome nach Nierentransplantation

QI-ID	Bezeichnung	Referenzbereich	Ergebnis 2014 [1]	Ergebnis 2013	Tendenz [2]
Indikatorengruppe: 3-Jahres-Überleben					
12237	3-Jahres-Überleben (bei bekanntem Status)	Nicht definiert	91,47 %	92,19 %	→
51562	3-Jahres-Überleben (Worst-Case-Analyse)	≥ 80,00 %	88,10 %	86,93 %	→
12811	Transplantatversagen innerhalb von 3 Jahren nach Nierentransplantation (bei bekanntem Status)	Nicht definiert	8,02 %	8,36 %	→
12741	Qualität der Transplantatfunktion (3 Jahre nach Transplantation)	Nicht definiert	94,74 %	94,93 %	→

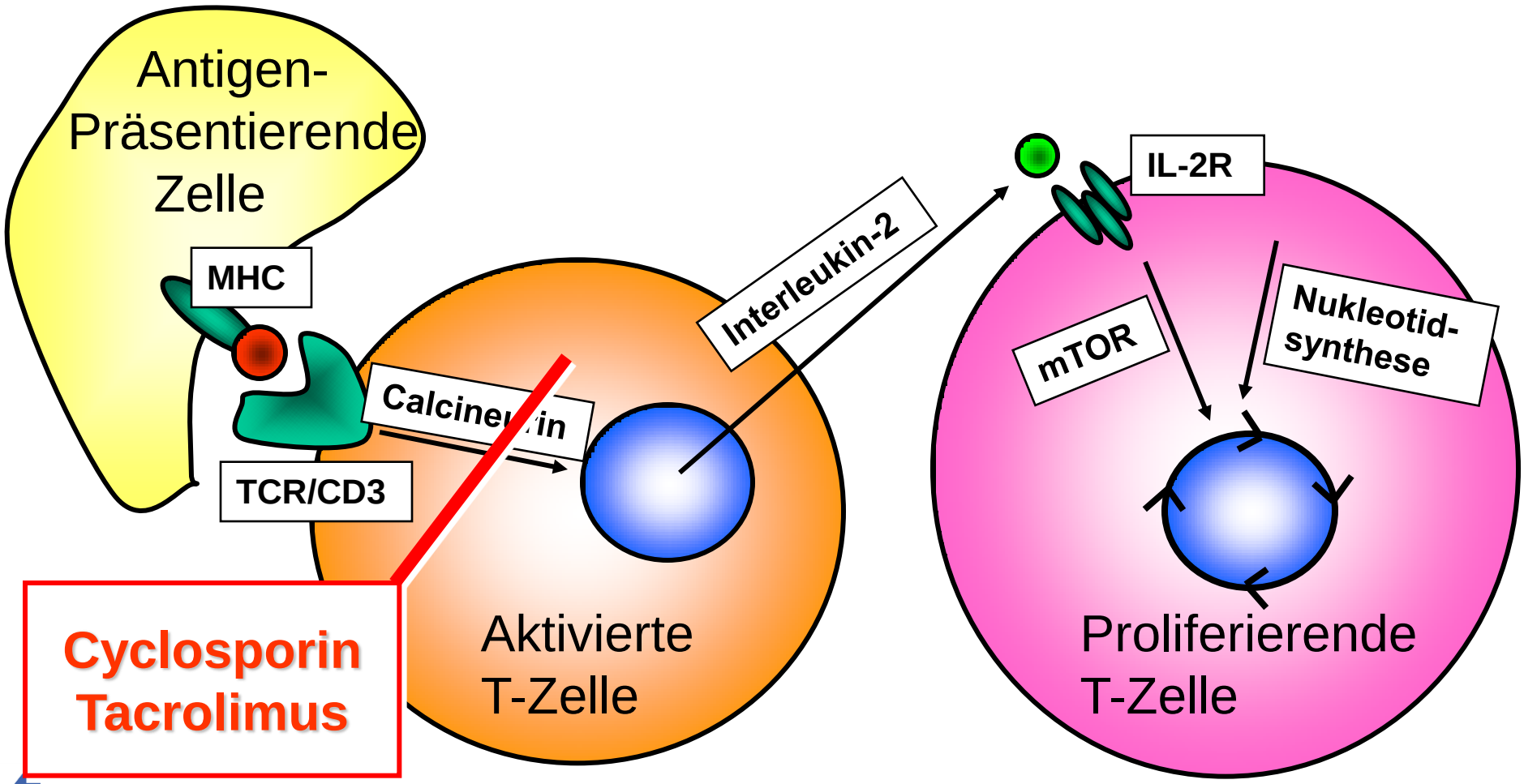
Molekulare Mechanismen der Abstossungsreaktion



Anti-T-Zell Antikörper (Induktionstherapie)

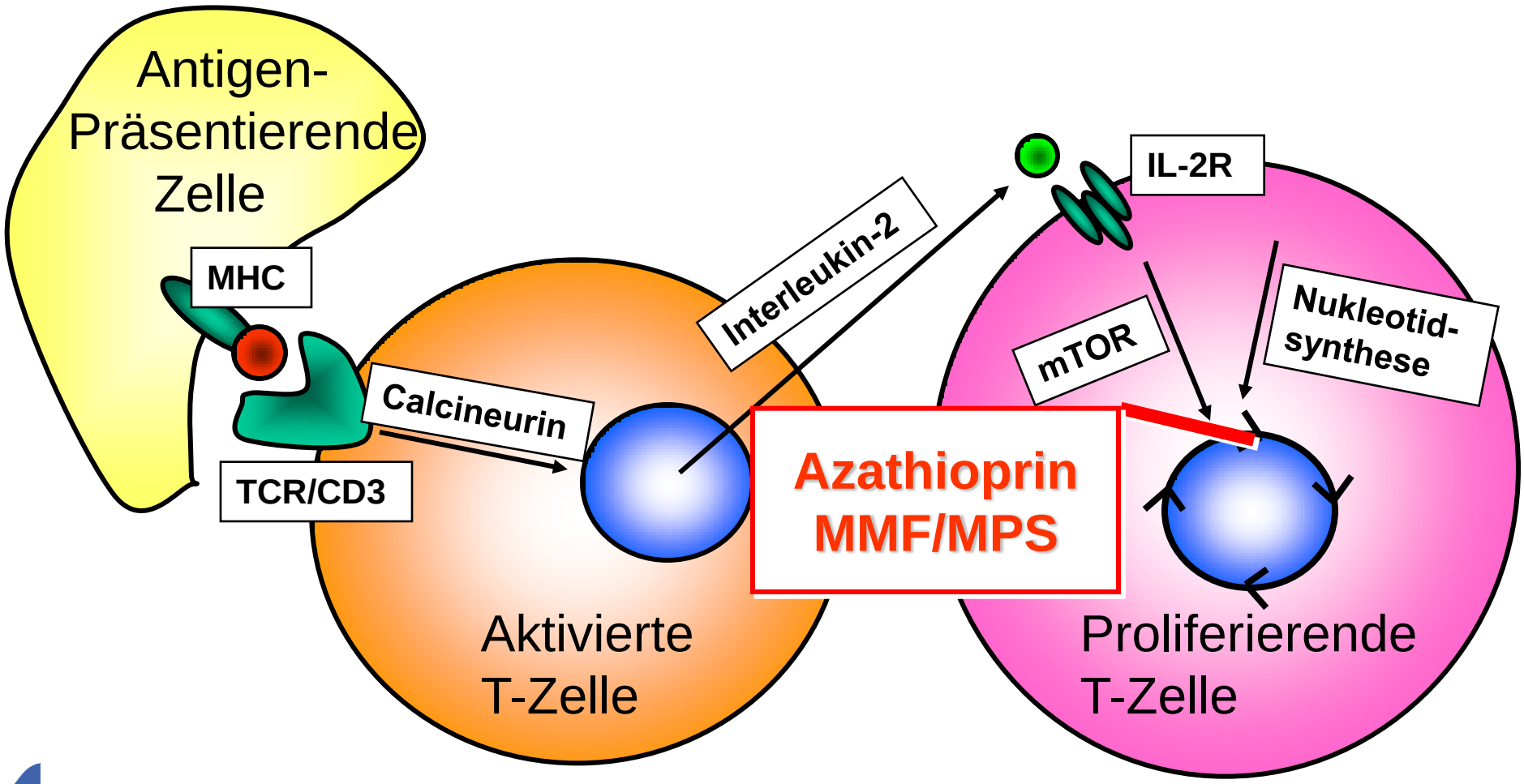


Calcineurin-Inhibitoren

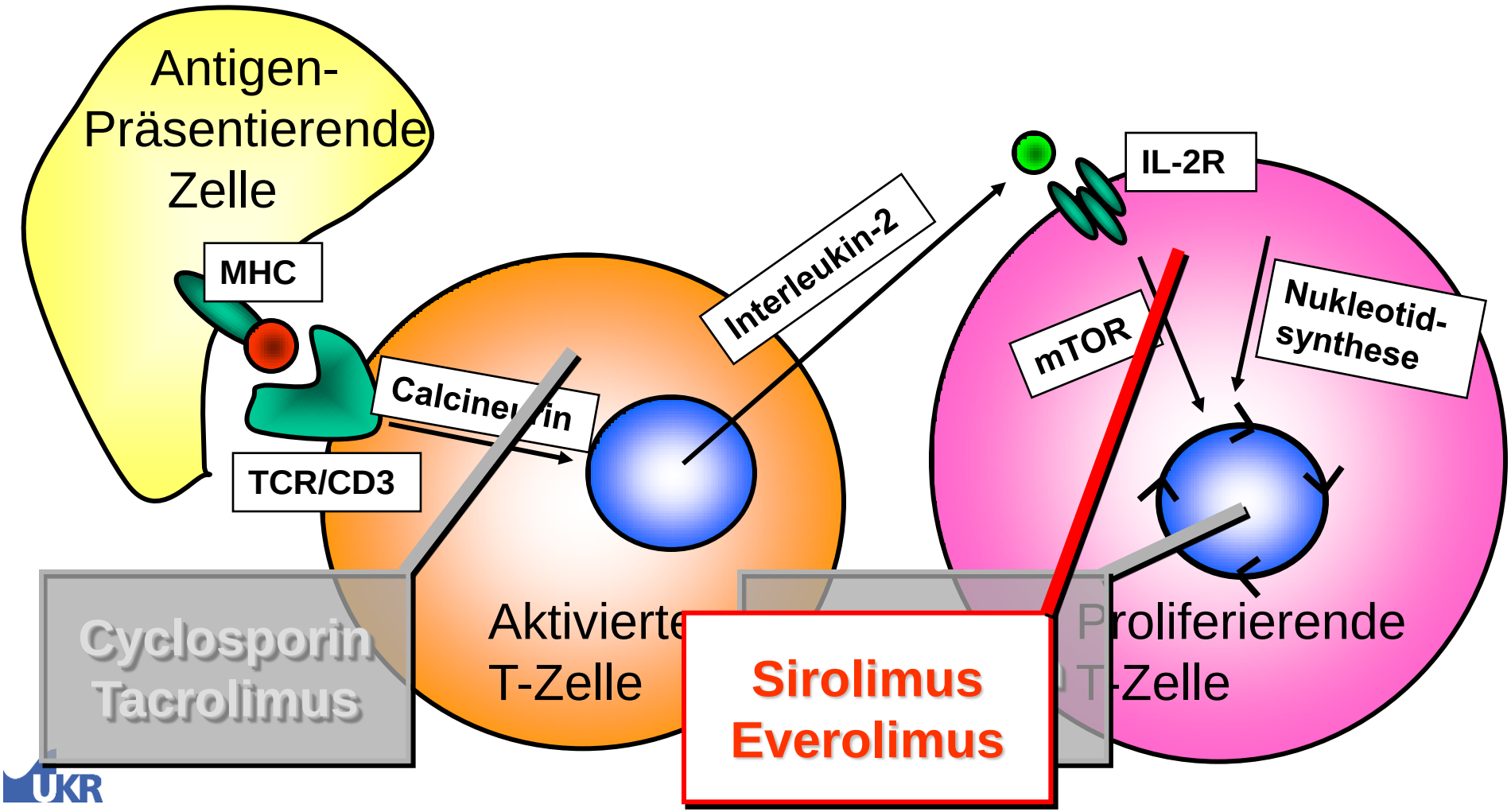


Cyclosporin
Tacrolimus

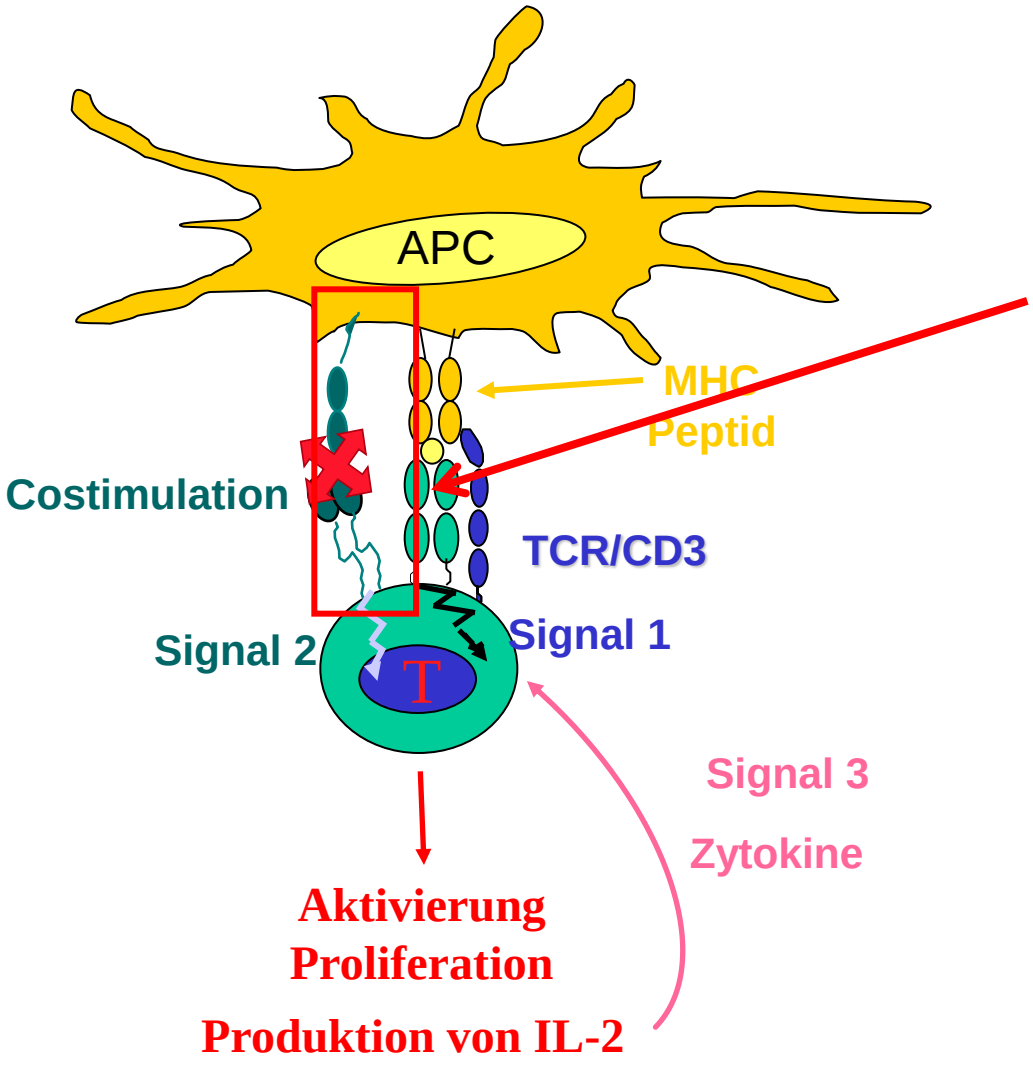
Proliferationsinhibitoren

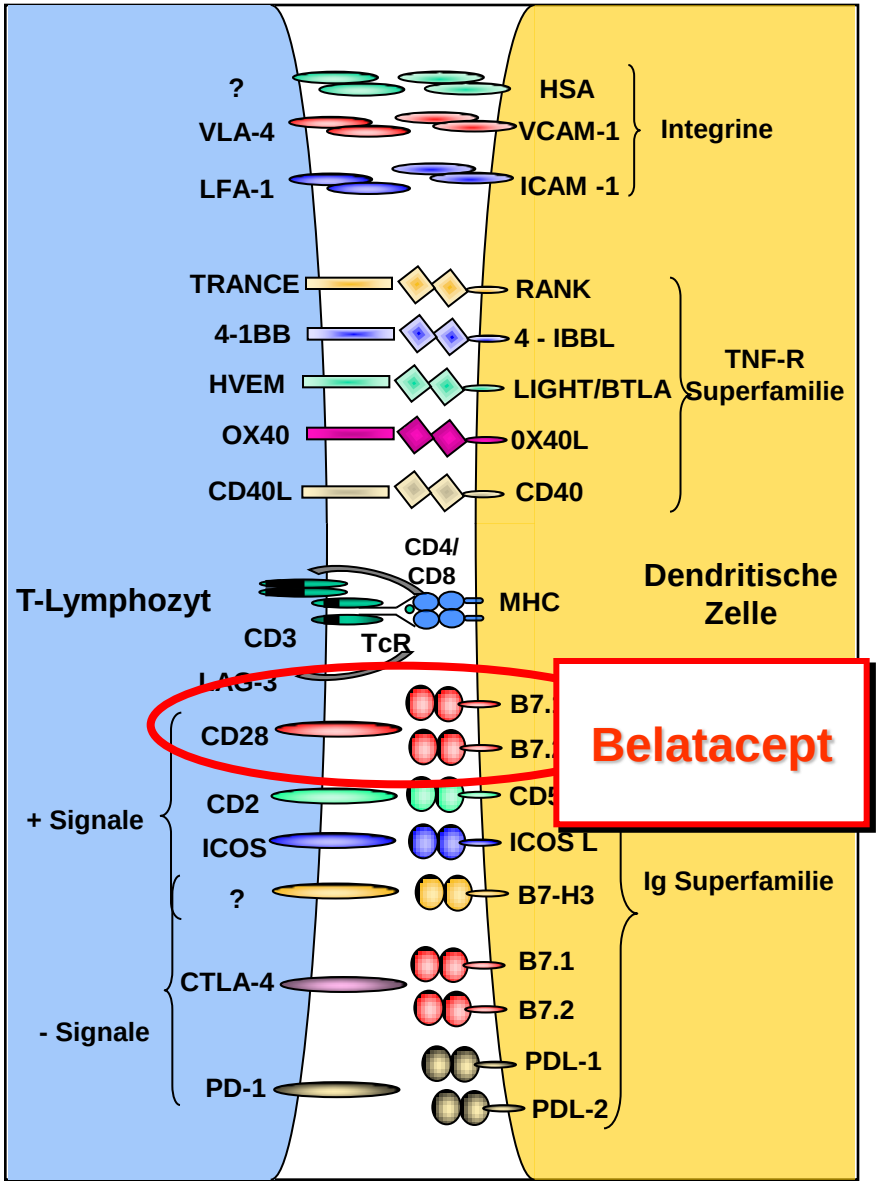


mTOR-Inhibitoren



Costimulations-Blocker



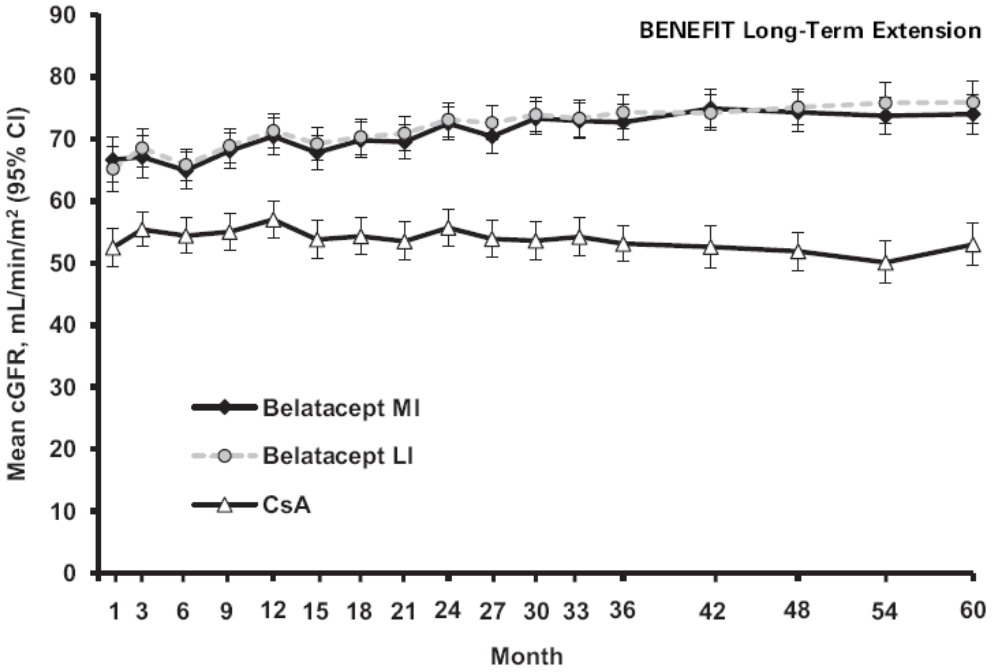


Belatacept

American Journal of Transplantation 2013; 13: 2875–2883
Wiley Periodicals Inc.

Long-Term Belatacept Exposure Maintains Efficacy and Safety at 5 Years: Results From the Long-Term Extension of the BENEFIT Study

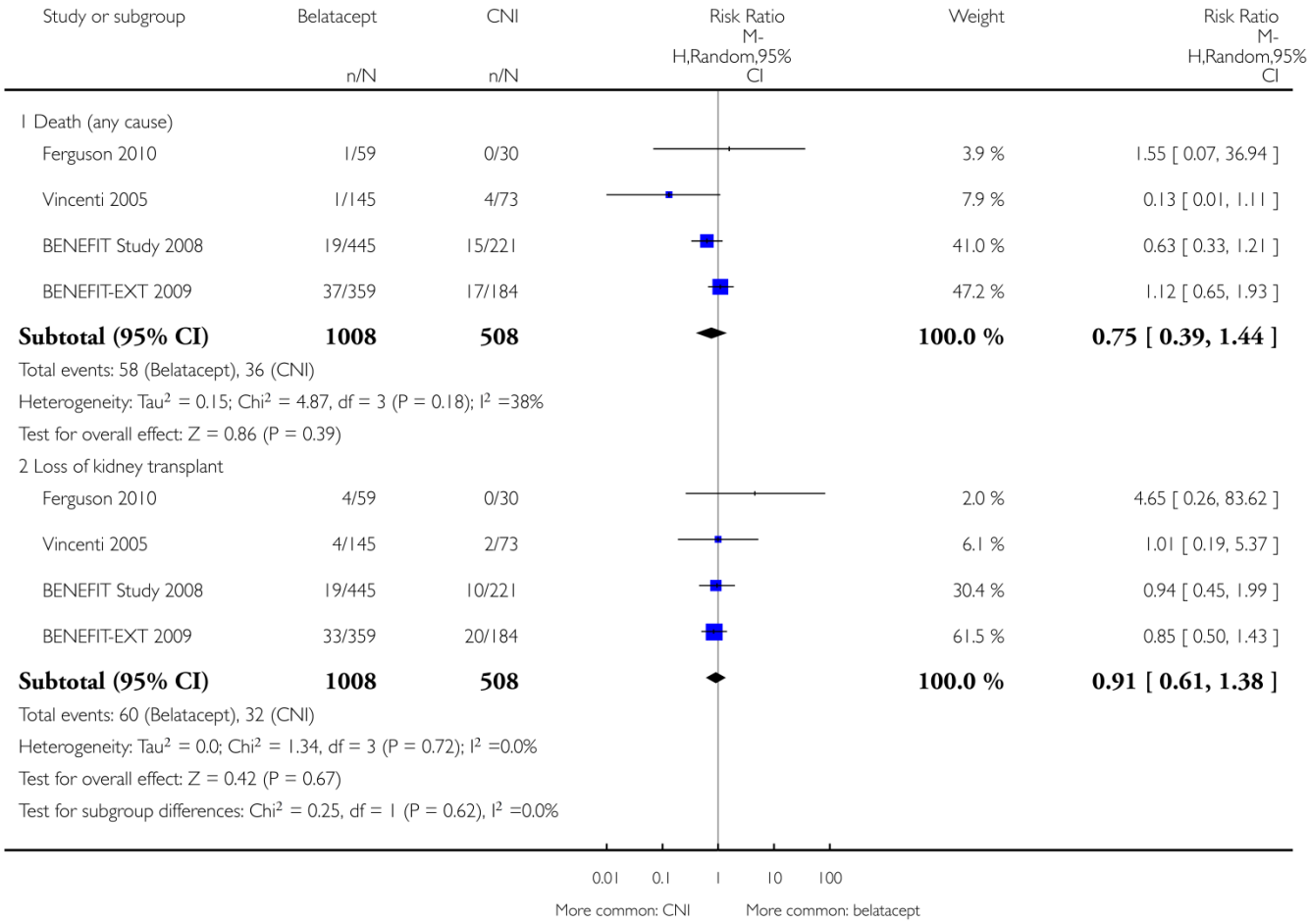
L. Rostaing[1,2,*], F. Vincenti[3], J. Grinyó[4], K. M. Rice[5], B. Bresnahan[6], S. Steinberg[7], S. Gang[8], L. E. Gaite[9], M.-C. Moal[10], G. A. Mondragón-Ramirez[11], J. Kothari[12], L. Pupim[13] and C. P. Larsen[14]



Patients with measurements

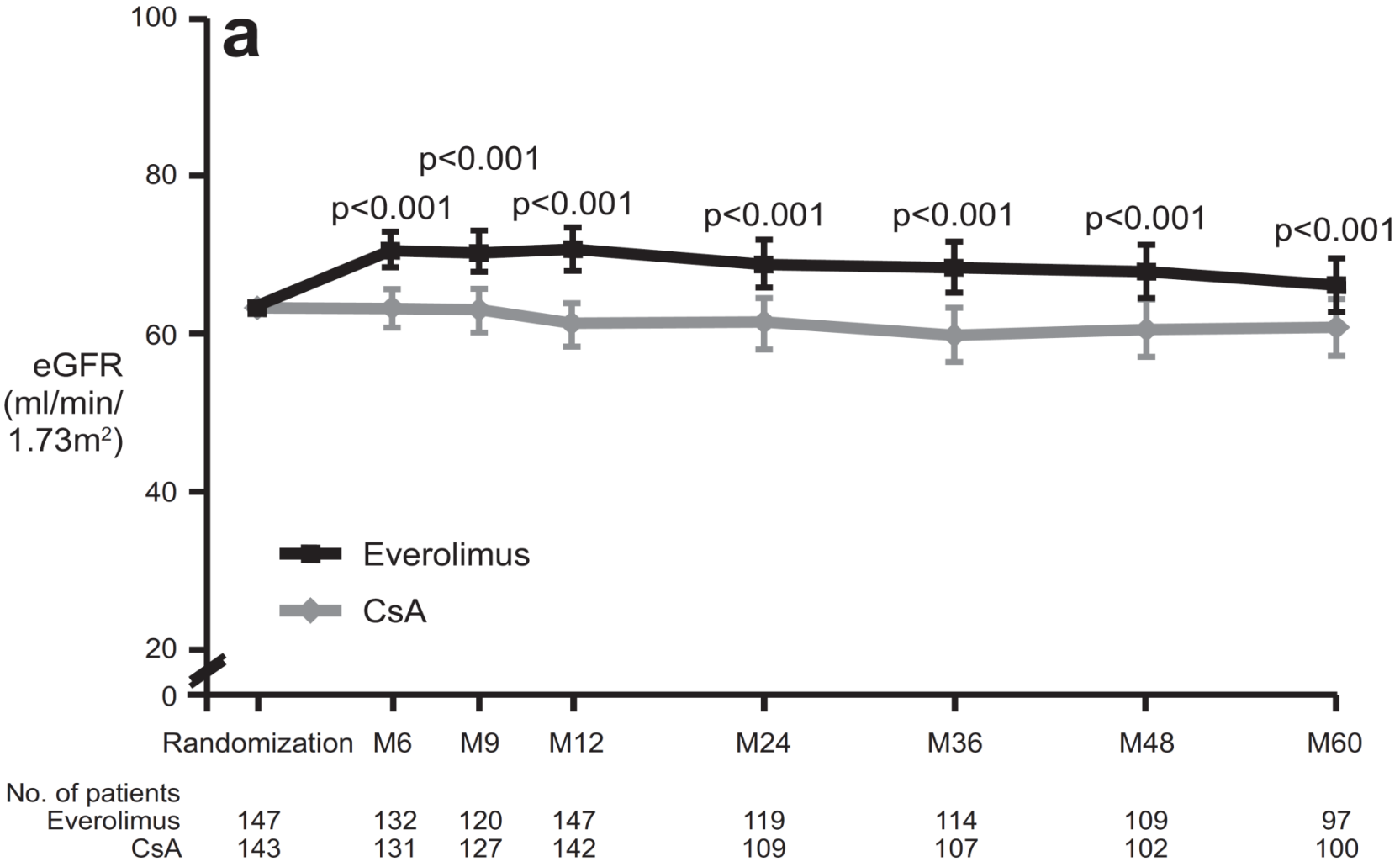
MI:	152	150	140	149	153	146	144	145	152	143	148	149	150	140	136	133	132
LI:	162	159	157	150	162	152	157	149	162	153	153	155	153	151	141	140	139
CsA:	134	132	126	123	129	127	122	122	129	125	125	123	129	113	107	102	98

Tod+graft loss: Belatacept wie Cyclosporin A



Masson P, Cochrane Database of Systematic Reviews 2014

Nierenfunktion: Everolimus vs. CyA



Budde K et al, AJT 2015

American Journal of Transplantation 2012; 12: 1192–1198
Wiley Periodicals Inc.

Donor-Specific HLA Antibodies in a Cohort Comparing Everolimus With Cyclosporine After Kidney Transplantation

L. Liefeldt[a,†,*], S. Brakemeier[a,†], P. Glander[a], J. Waiser[a], N. Lachmann[b], C. Schönemann[b], B. Zukunft[a], P. Illigens[a], D. Schmidt[a], K. Wu[a,c], B. Rudolph[c], H.-H. Neumayer[a] and K. Budde[a]

American Journal of Transplantation 2012; 12: 2561–2562
Wiley Periodicals Inc.

Letter to the Editor

J. Pascual[a] and W. Ams[b]

Does Everolimus Increase Donor-Specific HLA Antibodies in Kidney Transplant Recipients?

Clin Transplant 2013: 27: 455–462 DOI: 10.1111/ctr.12127

Nassim Kamar[a,b,c], Arnaud Del Bello[a,b], Nicolas Congy-Jolivet[b,d,e], Céline Guilbeau-Frugier[b,f], Isabelle Cardeau-Desangles[a], Marylise Fort[d], Laure Esposito[a], Joelle Guitard[a], Xavier Gamé[g] and Lionel Rostaing[a,b,c]

Incidence of donor-specific antibodies in kidney transplant patients following conversion to an everolimus-based calcineurin inhibitor-free regimen

TRANSFORM study

Open Access Journal of Clinical Trials 2014:6

Pascual et al

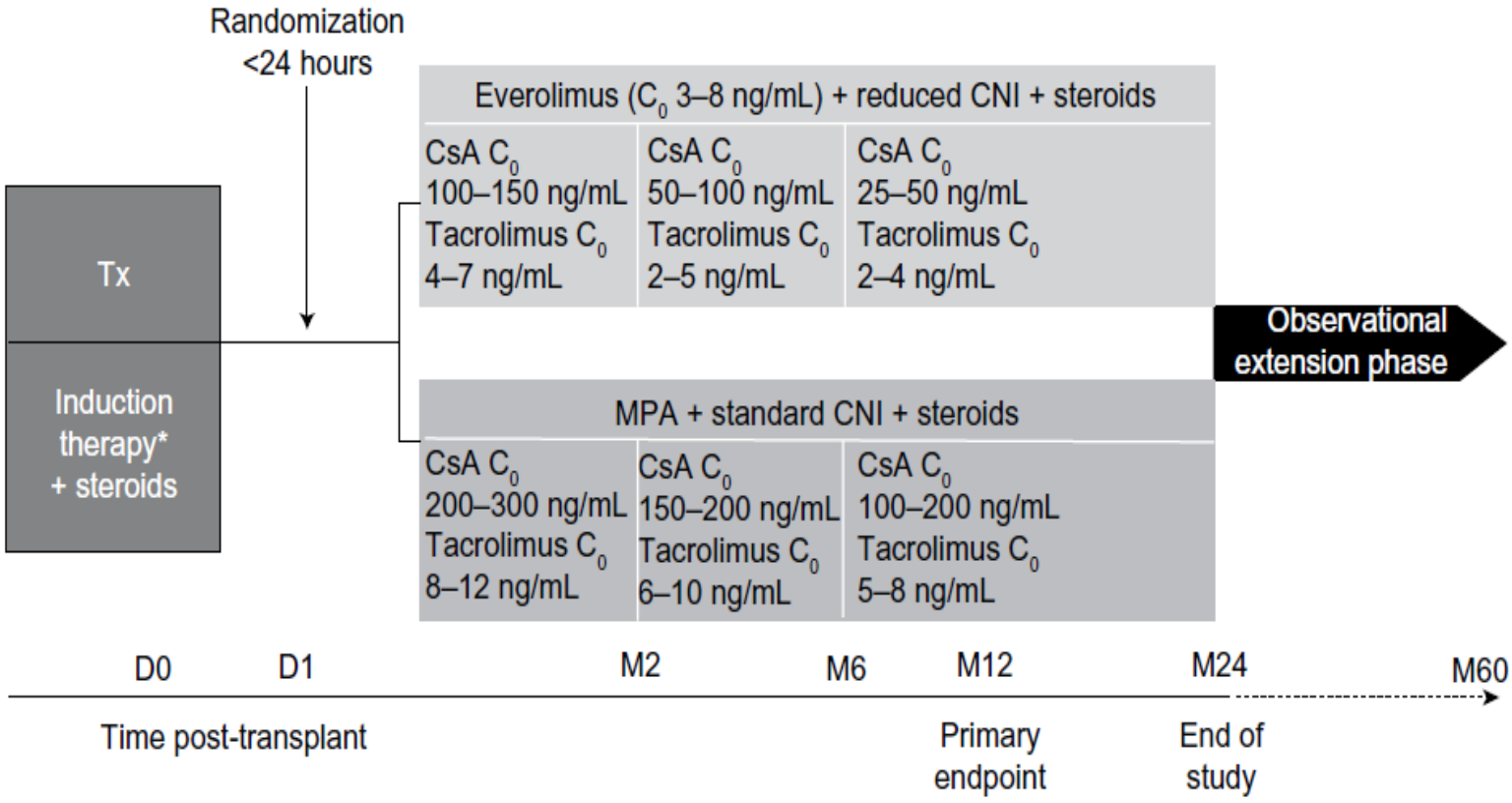


Figure 1 TRANSFORM study design.

Induktionstherapie: wo stehen wir?

1.1: We recommend starting a combination of immunosuppressive medications before, or at the time of, kidney transplantation. *(1A)*

1.2: We recommend including induction therapy with a biologic agent as part of the initial immunosuppressive regimen in KTRs. *(1A)*

1.2.1: We recommend that an IL2-RA be the first-line induction therapy. *(1B)*

1.2.2: We suggest using a lymphocyte-depleting agent, rather than an IL2-RA, for KTRs at high immunologic risk. *(2B)*

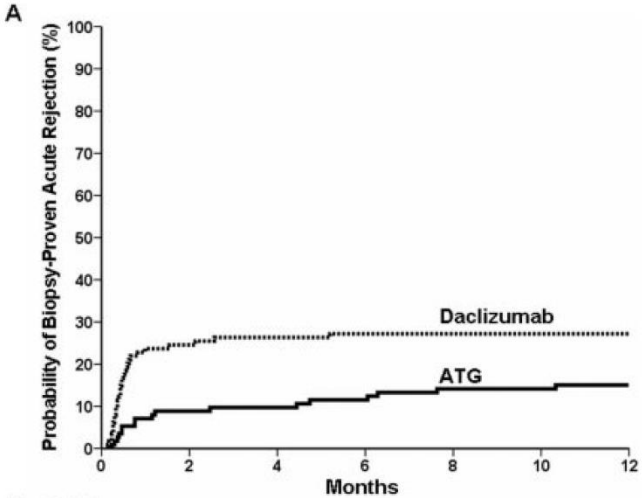
KDIGO 2009; AJT 2009;S3

IL2-RA besser als Placebo
IL2-RA vs. ATG → ??

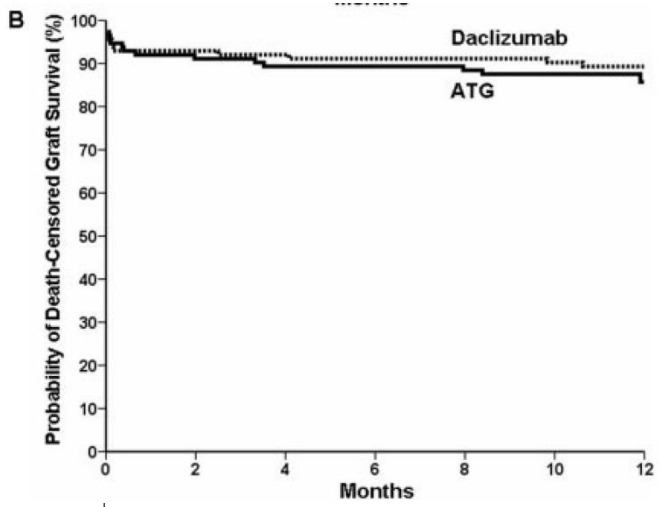
	IL2RA vs. Placebo (1 yr)	IL2RA vs. Placebo (3 yr)	IL2RA vs. ATG (1 yr)	IL2RA vs. ATG (3-5 yr)
Biopsy-proven rejection	**0.72 (0.64-0.81), n=3898**	NA	**1.3 (1.01-1.67), n=1106**	1.77 (0.98-3.18), n=183
Graft loss (death censored)	**0.75 (0.6-0.93), n=4672**	1.07 (0.71-1.59), n=695	0.98 (0.66-1.45), n=1394	2.04 (0.19-21.79), n=99
Mortality	0.77 (0.54-1.10), n=4647	0.62 (0.3-1.29), n=695	1.31 (0.77-2.25), n=1609	1.79 (0.58-5.51), n=339
Malignancy	0.87 (0.46-1.67), n=3898	0.83 (0.45-1.53), n=635	**0.25 (0.07-0.87), n=1067**	0.67 (0.15-2.91), n=339
CMV	**0.81 (0.68-0.97), n=3169**	1.0 (0.26-4.72), n=100	**0.68 (0.5-0.93), n=1647**	1.31 (0.26-6.56), n=223

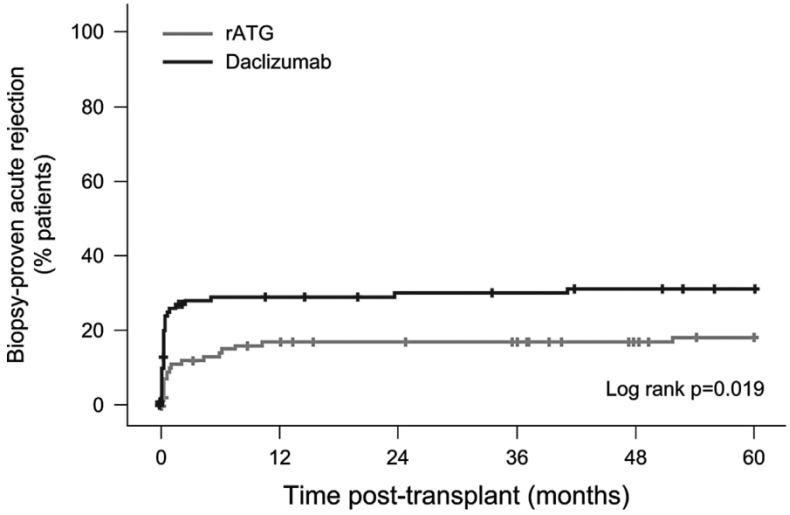
Webster et al, Cochrane Database of Systematic Reviews 2010, Issue 1

Thymoglobulin:
weniger akute Rejektion,
aber kein Einfluss auf 1- oder 5-Jahres-Tx-Überleben

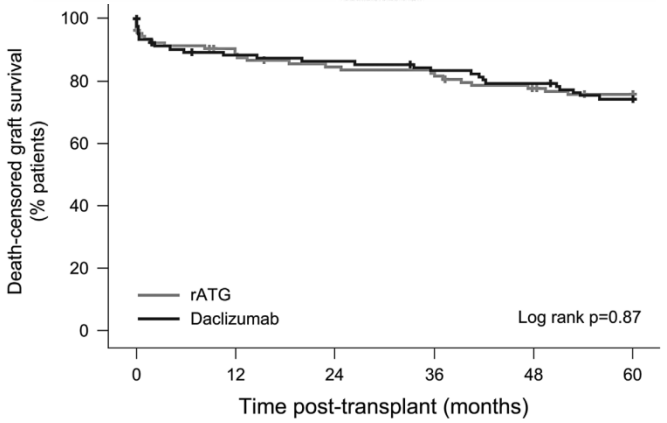


1 Jahr



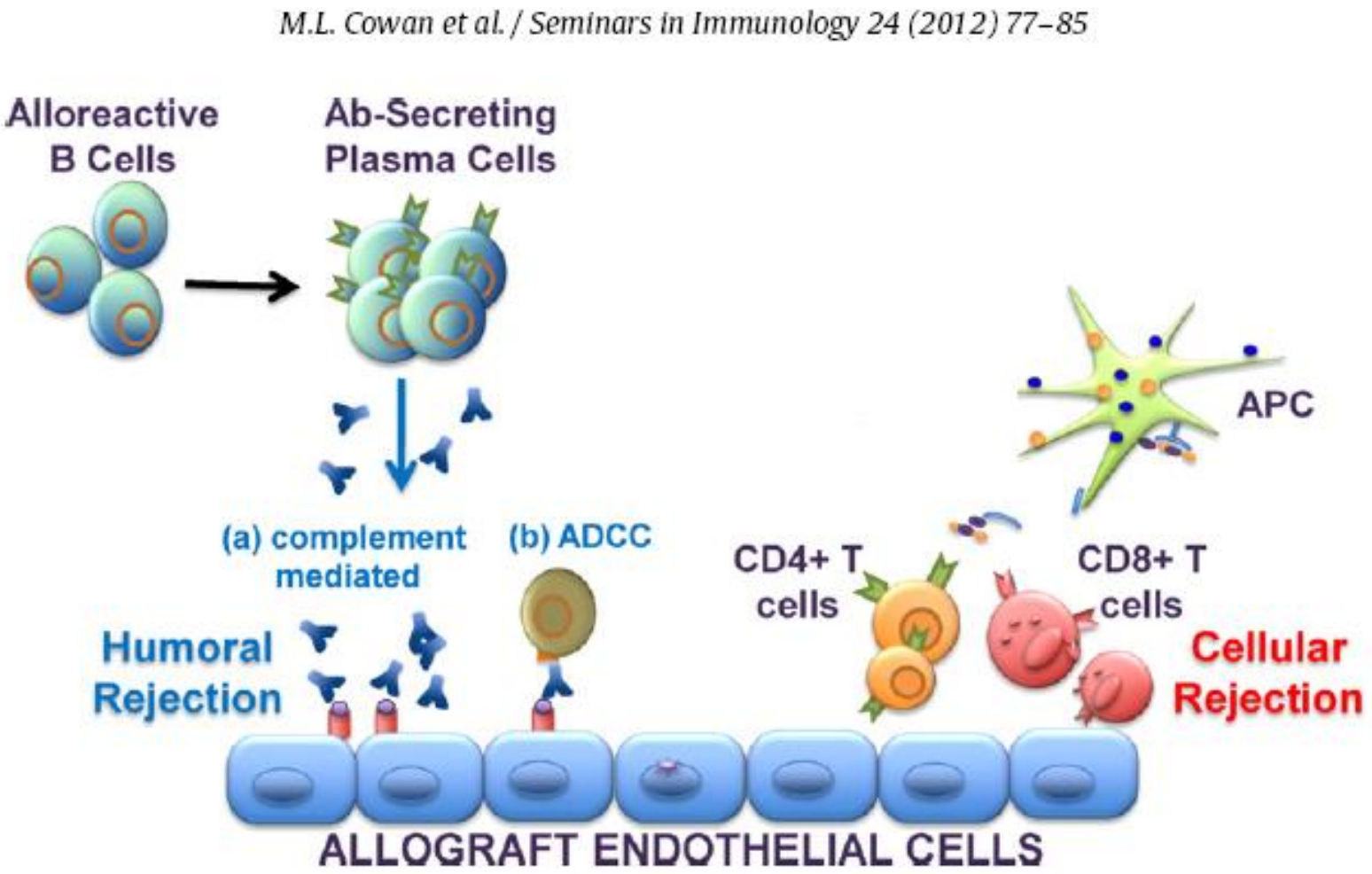


5 Jahre

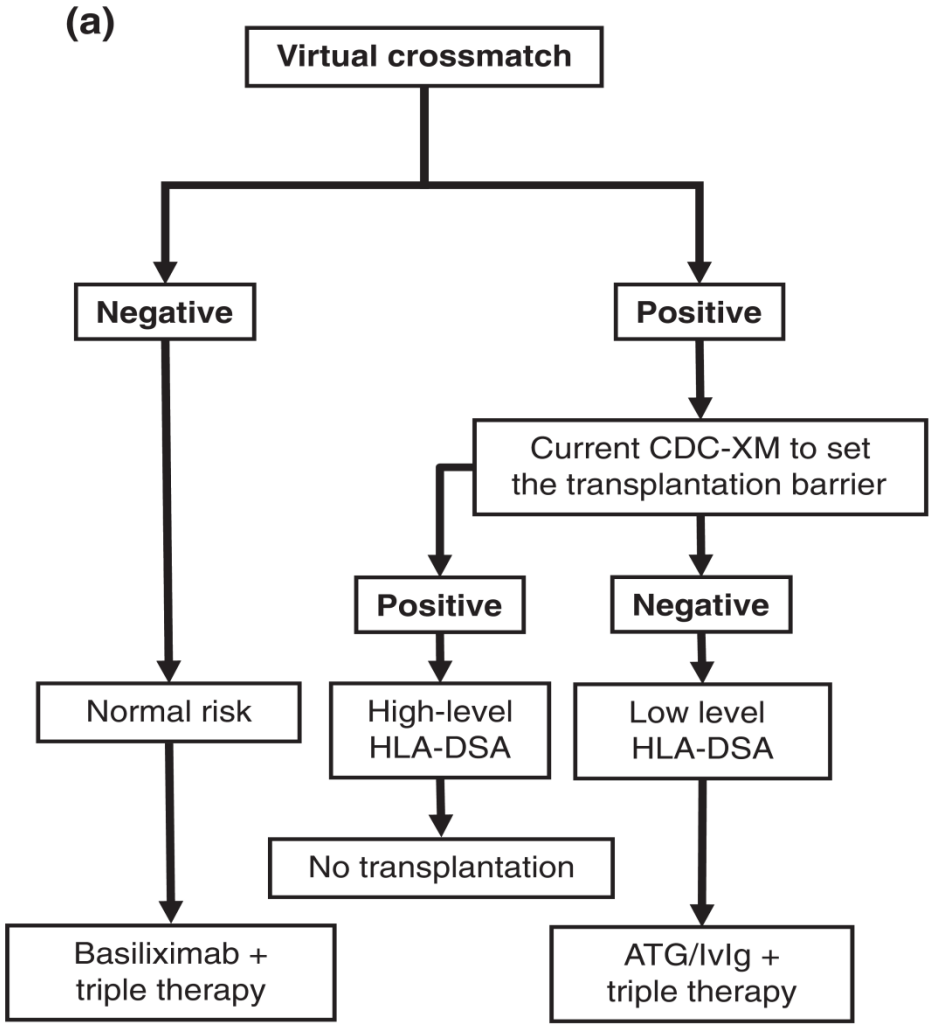


Hellemans et al, AJT 2015 Noel et al, JASN 2009

Akute Rejektion
Humoral / Zellulär



„Basel approach“



- **Virtual XM neg**: Basiliximab
- **Virtual XM pos (=MFI>500) <u>und</u> CDC-XM neg**: ATG-Fresenius 9mg/kg prä-NTX, dann 3mg/kg für 4d, zusätzl IVIG 1.6g/kg über 4d

Amico et al, TI 2011

UKR-Vorschlag Induktionsschema bei ABOc

- **Niedriges immunologisches Risiko**: Basiliximab 20mg d0, d4
  Definition:
  - CDC-PRA <30% und nie DSA im Luminex
- **Hohes immunologisches Risiko**: Thymoglobulin 4x1.5mg/kg;
  Definition (mind. 1 der folgenden):
  - Alter ≤65a *und* mind. 1x DSA (MFI>500)* (unabhängig von CDC-PRA)
  - CDC-PRA≥30% aktuell oder historisch (unabh. von Alter oder DSA)
  - Re-NTX mit frühem immunolog. Verlust einer vorigen NTX (<2a) (unabh. von Alter oder DSA)
  - Re-NTX mit „Repeat HLA-Antigen“(unabh. von Alter oder DSA)
- **Kontraindikation**: positives CDC-Cross Match

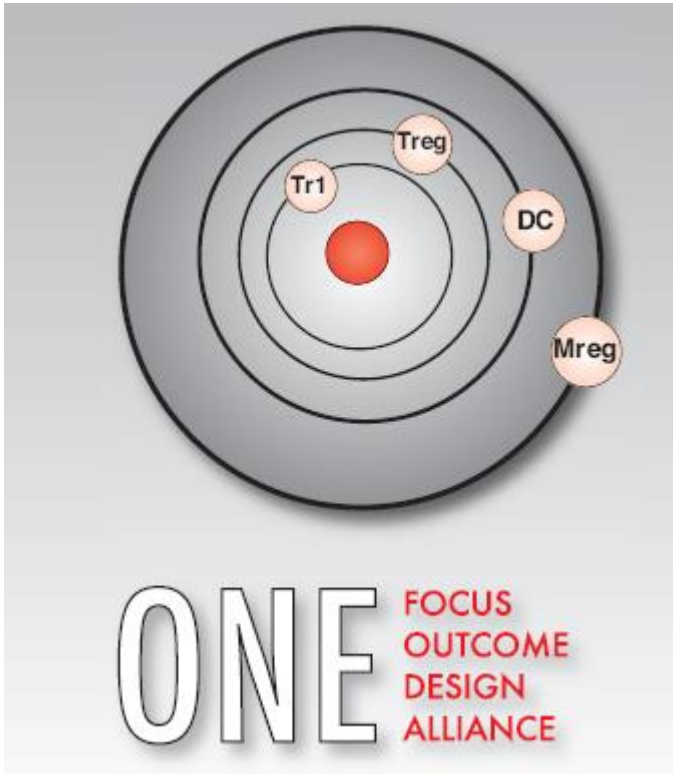
* Alter>65a: Einzelfallentscheidung (biologisches Alter, AZ, weitere Risikofaktoren wie DGF-Risiko, DSA Klasse I und II)

Welche aktuellen Entwicklungen haben Chancen echte Neuigkeiten zu werden?

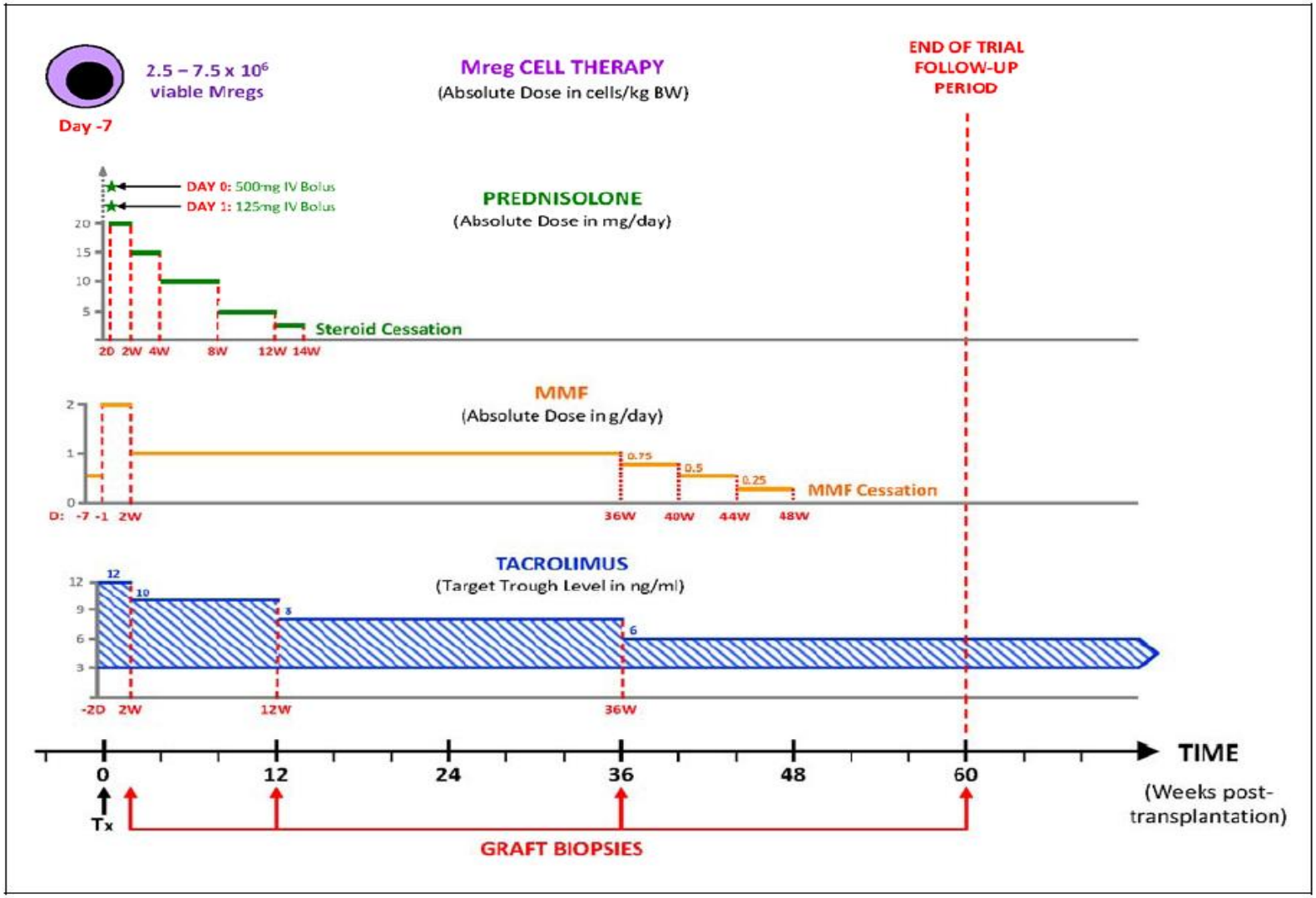
The ONE study

ONE STUDY

A Unified Approach to Evaluating
Cellular Immunotherapy
in Solid Organ Transplantation



The ONE study

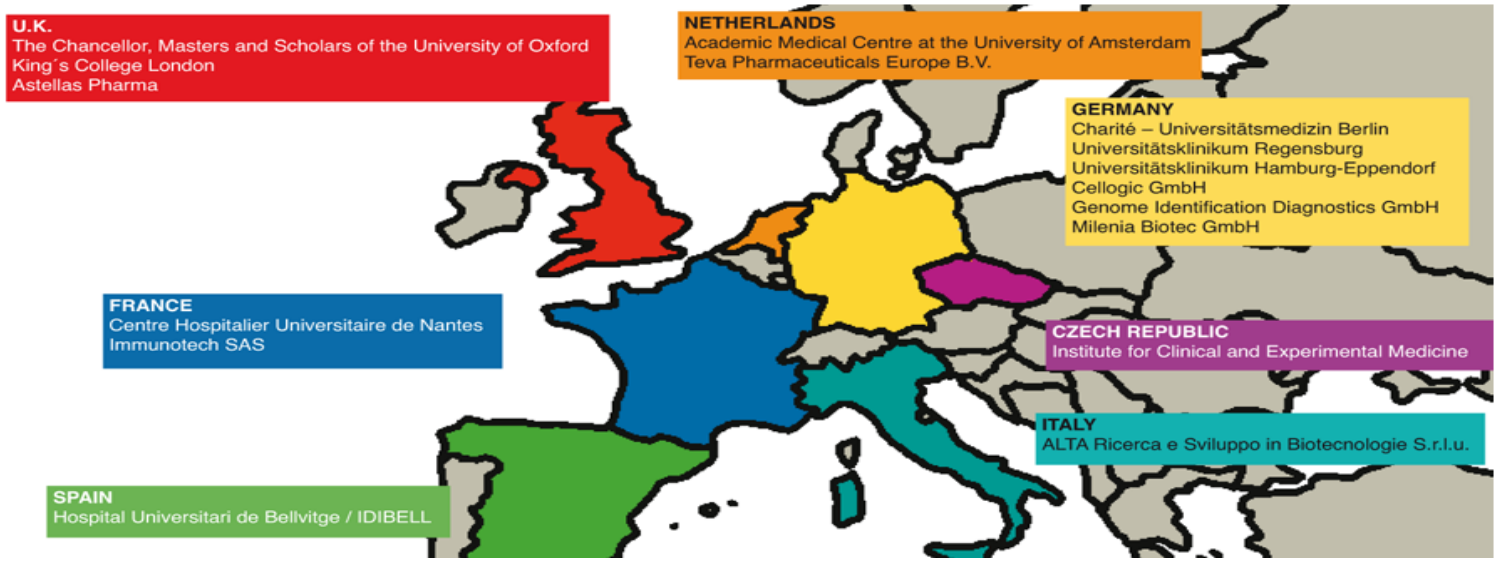


BIODrIM

Home | Description | Objectives | Beneficiaries | Publications

Project beneficiaries

The *BIO-DrIM* consortium is made up of sixteen partners, of which seven are clinical institutions, two are academies, three are research-performing SMEs (Cellogic, GenID and Milenia), one is a SME expert in services for the RTD activities (ALTA) and three are big companies (Astellas, TEVA and Beckman Coulter - Immunotech). Seven countries are represented: Germany, France, Italy, the United Kingdom, the Netherlands, Czech Republic and Spain. The participating groups have been chosen for their scientific excellence, technical expertise, experience in translational research, and for their managerial skills.



STUDY 4: Perioperative Biomarker-based stratification into low/high responder after kidney transplantation.

The Study **CELLIMIN (Prospective donor-specific Cellular alloresponse assessment for Immunosuppression Minimization in de novo renal transplantation)** is an international multicentre open label randomized non-inferiority Phase II clinical trial for selection of low anti-donor T-cell responders using the IFN-γ ELISPOT assay as biomarker for patient stratification before transplantation to safely receive long-term drug minimization based on **IS** (tacrolimus) **monotherapy**. The **perioperative stratification** of patients into low/high-responders will demonstrate the clinical utility of the **IFN-γ ELISPOT** (Enzyme-Linked ImmunoSpot).

American Journal of Transplantation 2013; 13: 1880–1890
Wiley Periodicals Inc.

Cross-Validation of IFN-γ Elispot Assay for Measuring Alloreactive Memory/Effector T Cell Responses in Renal Transplant Recipients

O. Bestard[1,2,*], E. Crespo[2,†], M. Stein[3,4,†], M. Lúcia[2,†], D. L. Roelen[5], Y. J. de Vaal[5], M. P. Hernandez-Fuentes[6], L. Chatenoud[7], K. J. Wood[8], F. H. Claas[5], J. M. Cruzado[1,2], J. M. Grinyó[1,2], H. D. Volk[4] and P. Reinke[3,4]

American Journal of Transplantation 2011; 11: 156–162
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2010.03352.x

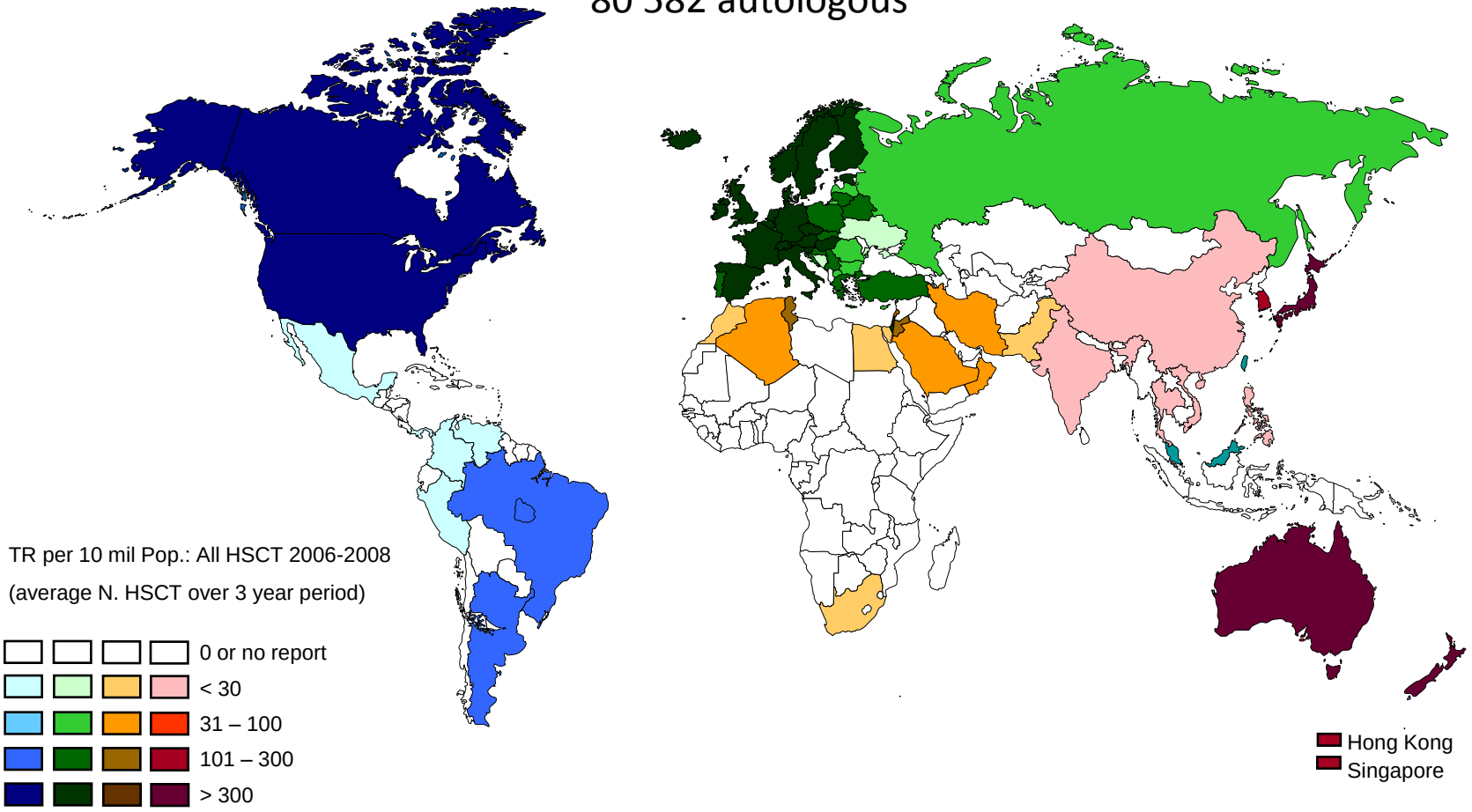
Case Report

Kidney Transplant from the Same Donor without Maintenance Immunosuppression after Previous Hematopoietic Stem Cell Transplant

J. Fangmann[a,*], H. Kathrin Al-Ali[b], U. Sack[c], M. Kamprad[d], H. M. Tautenhahn[e], S. Faber[f], J. Hauss[e], D. Niederwieser[b], T. Lindner[g] and A. Bachmann[g]

146 808 HSCT's 2006 – 2008

66 226 allogeneic
80 582 autologous



Worldwide Network for Blood and Marrow Transplantation

Gratwohl et al, Haematologica, 2013

Review

Biol Blood Marrow Transplant 20 (2014) 440–449

Immune Reconstitution after Haploidentical Hematopoietic Stem Cell Transplantation

Ying-Jun Chang [1], Xiao-Yu Zhao [1], Xiao-Jun Huang [1,2,*]

[1] *Peking University People's Hospital and Peking University Institute of Hematology, Beijing Key Laboratory of Hematopoietic Stem Cell Transplantation, Beijing, China*
[2] *Peking-Tsinghua Center for Life Sciences, Beijing, China*

A B S T R A C T

Haploidentical hematopoietic stem cell transplantation (HSCT) offers the benefits of rapid and nearly universal donor availability and has been accepted worldwide as an alternative treatment for patients with hematologic malignancies who do not have a completely HLA-matched sibling or who require urgent transplantation.

Zusammenfassung

In Deutschland werden die meisten Patienten mit der klassischen immunsuppressiven Kombination

Calcineurininhibitor, MMF/MPS, Steroide +/- IL2R-Blocker

behandelt.

Der Stellenwert der **mTOR-Inhibitoren** wird zunehmend besser definiert.

Co-Stimulationsblocker werden noch wenig eingesetzt.

Aktuell untersucht werden

- Eine Zell-basierte Immunomodulation des Empfängers,
- Eine Risiko-stratifizierte individuelle Immunsuppression,
- Eine Induktion eines Empfänger-Chimerismus durch haploidente Stammzelltransplantation

Vielen Dank für Ihr Interesse

UKR

Universitätsklinikum
Regensburg