Swisstolerance.CH - kombinierte Nieren- und Stammzelltransplantation zur Toleranzinduktion

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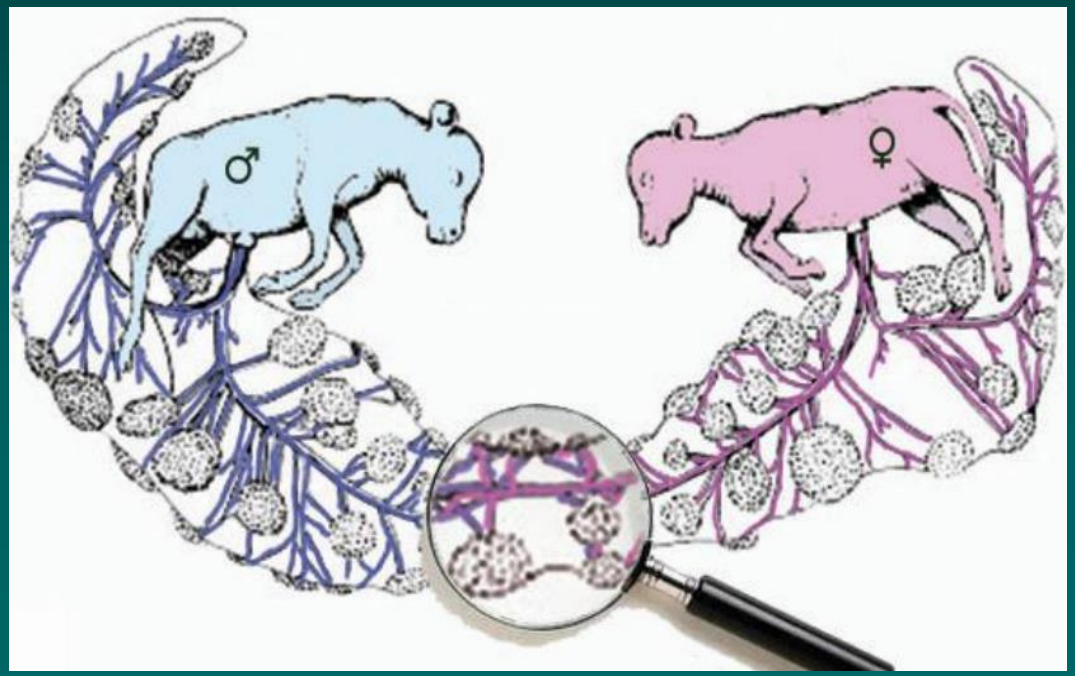
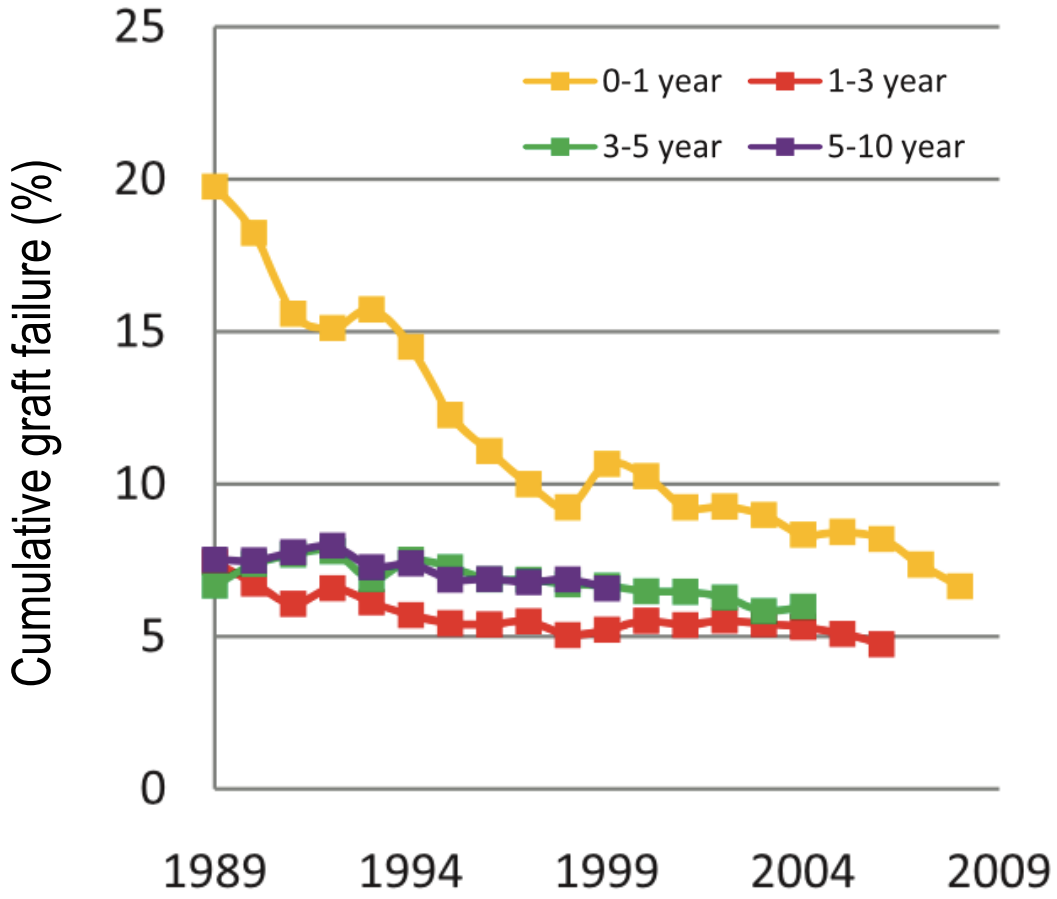


Topics

- **Part I – General background on mixed chimerism and tolerance**
  - Why tolerance induction?
  - How to induce tolerance?
  - Overview on mixed chimerism trials
- **Part II – Swisstolerance.CH trial**
- **Part III – Future directions**

Late kidney allograft loss



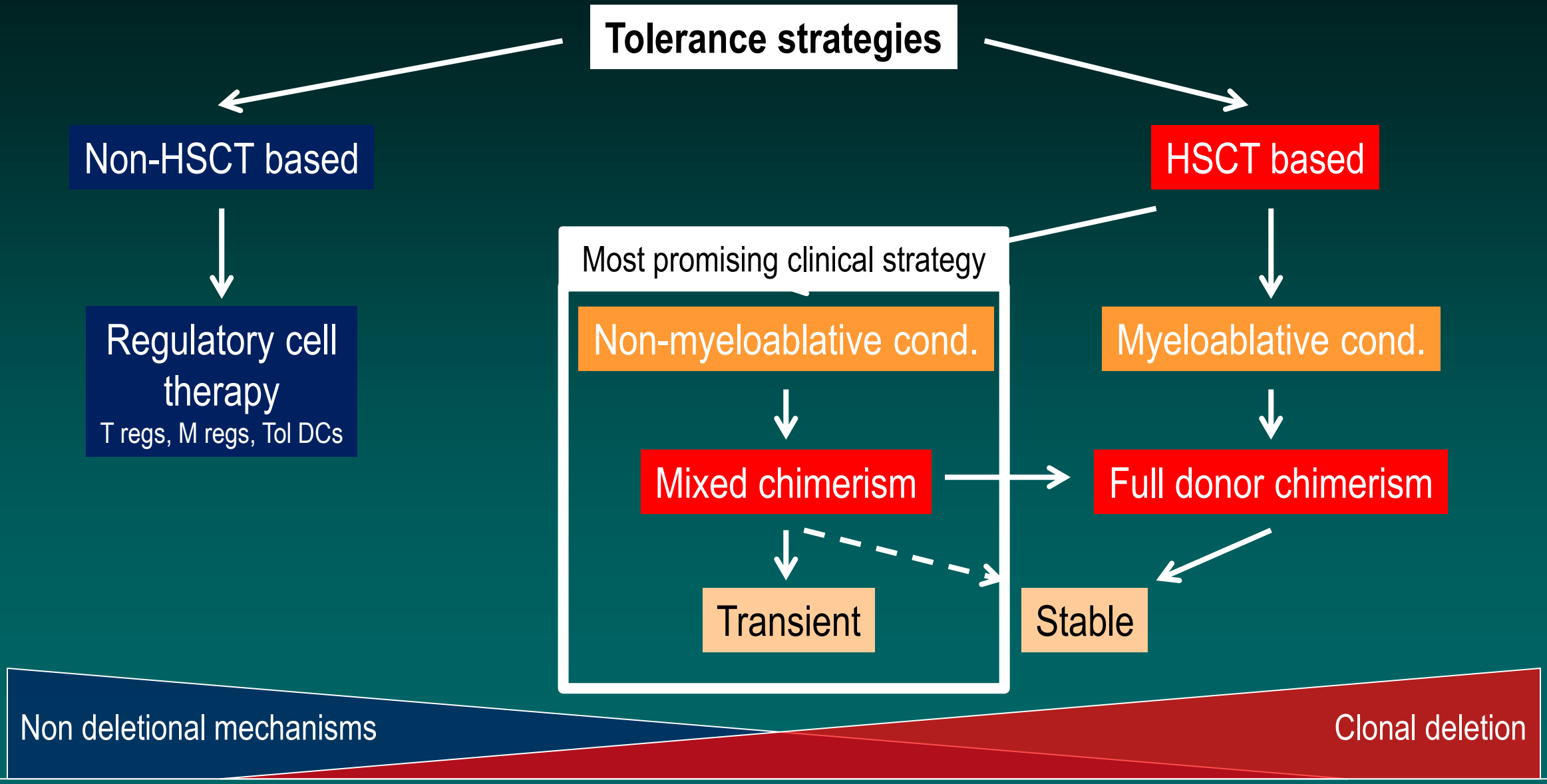
Reasons for late allograft loss:

- Chronic rejection *
- Drug toxicity *
- Acute rejection * (due to non-adherence)
- BKV nephropathy *
- Recurrent disease

*** could be prevented by induction of donor-specific tolerance**

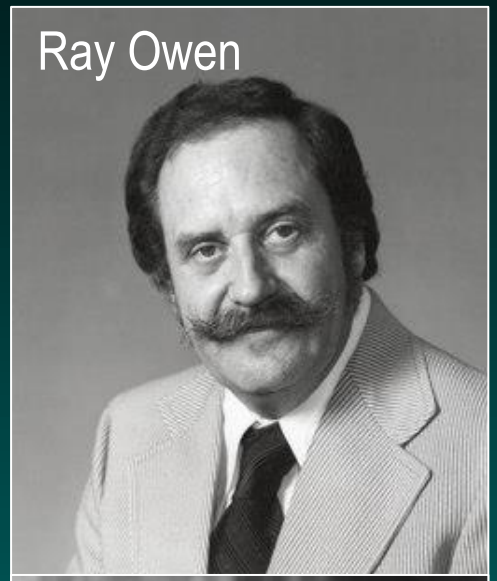
Lamb, *Am J Transplant* 2011; Pascual, NEJM 2002

Tolerance strategies in solid organ transplantation



(HSCT = hematopoietic stem cell transplantation)

Mixed chimerism & tolerance – seminal research



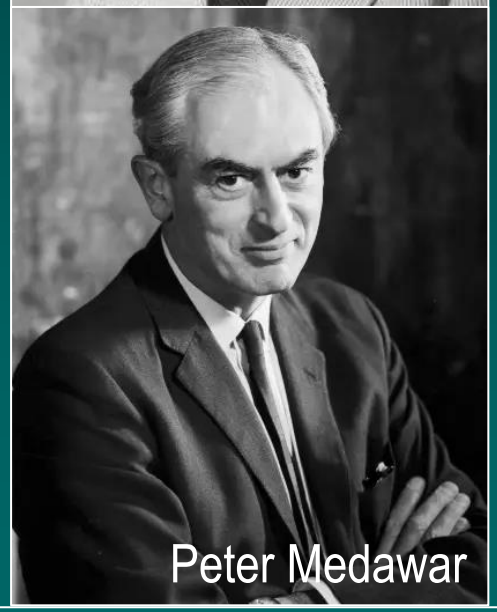
Reprinted from *Science* **102**:400–401 (1945)

IMMUNOGENETIC CONSEQUENCES OF VASCULAR ANASTOMOSES BETWEEN BOVINE TWINS[1]

Ray D. Owen

[1] From the Departments of Genetics (No. 346) and Veterinary Science, University of Wisconsin, in cooperation with the Bureau of Animal Industry, U. S. Department of Agriculture.

Several interesting problems in the fields of genetics, immunology and development are suggested by these observations. Most of them are still largely speculative and will not be considered here. An ap-



No. 4379 October 3, 1953 NATURE 603

'ACTIVELY ACQUIRED TOLERANCE' OF FOREIGN CELLS

By Dr. R. E. BILLINGHAM*, L. BRENT and Prof. P. B. MEDAWAR, F.R.S.

Department of Zoology, University College, University of London

THE experiments to be described in this article provide a solution—at present only a 'laboratory' solution—of the problem of how to make tissue homografts immunologically acceptable to hosts which would normally react against them. The principle underlying the experiments may be expressed in the following terms: that mammals and birds never develop, or develop to only a limited degree, the power to react immunologically against foreign homologous tissue cells to which they have been exposed sufficiently early in fœtal life. If, for example, a fœtal mouse of one inbred strain (say, *CBA*) is inoculated *in utero* with a suspension of living cells from an adult mouse of another strain

pigmentation of the cells into which they ultimately develop. Unfortunately, experiments with embryonic melanoblasts, having been done with quite different purposes in mind, do not make it possible to decide whether survival into adult life is due to an antigenic adaptation of embryonic cells which have been obliged to complete their development in genetically foreign soil, or whether it is due to a suppression or 'paralysis'[2] of the host's immunological response.

An exactly comparable phenomenon has been described by Owen[3], who found that the majority of dizygotic cattle twins are born with, and long retain, red blood cells of dizygotic origin: each calf contains a proportion of red cells belonging genetically to

Owen, Science 1945; Billingham/Brent/Medawar, Nature 1953

Three centers in the US

- **Around 100 patients worldwide, in whom intentional tolerance to a renal allograft has been induced by mixed chimerism.**

New centers (since 2015)

- Zurich (Fehr et al, Pub 2022)
- South Corea (Kwon, Lee et al; Pub 2021)
- Tel Aviv (Mor et al; no publication)

Characteristics of the three US protocols

	Sachs / Boston	Strober / Stanford	Ildstad / Chicago
HLA match	HLA-matched & HLA-mismatched	HLA-matched *(HLA-mismatched not successful yet)*	HLA-matched & HLA-mismatched
Conditioning	Pretransplant	Posttransplant	Pretransplant
Irradiation	Thymic irradiation	Total lymphoid irradiation	Total body irradiation
Chemotherapy	Cyclosphospamide	None	[illegible]ide
T cell depletion	Siplizumab (anti-CD2)	Anti-thym[illegible]	None
B cell depletion	Rituximab		None
Cellular transplant	Bon[illegible] (unm[illegible])	[illegible]bilized peripheral stem cells (T-cell depletion and defined add-back)	Mobilized peripheral stem cells + «facilitating cells» (CD8+/TCR-)
Chimerism	Mixed, mostly transient	Mixed, some transient	Full donor in majority
*GvHD; CTS; TRM **	No; Yes; No	No; No; No	Yes; No; Yes
Recurrent disease	Usual risk	Usual risk	Lower risk?

Success rate: around 70%

**CTS = chimerism transition syndrome; TRM = Transplant-related mortality*

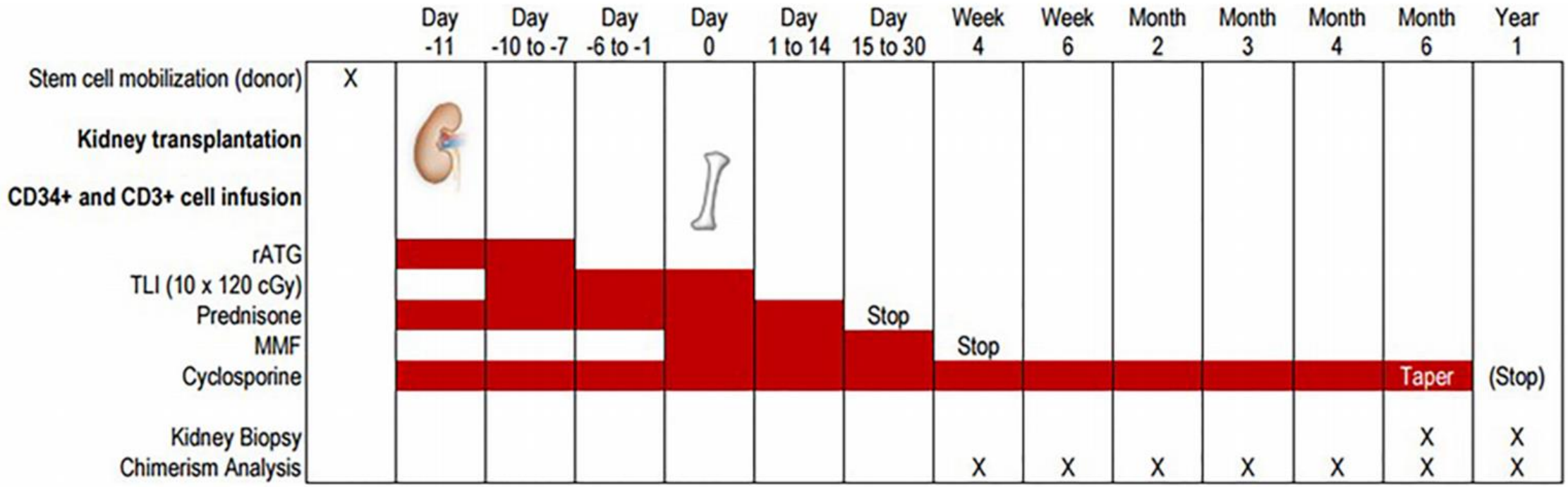
Kawai, NEJM 2013; Scandling, AJT 2012; Leventhal, Science Translat Med 2012

Topics

- **Part I – General background on mixed chimerism and tolerance**
- **Part II – Swisstolerance.CH trial**
  - Protocol
  - Results
  - Is it donor-specific tolerance?
- **Part III – Future directions**

Swisstolerance.CH – Protocol

- **Standford HLA-matched protocol**
  - Posttransplant conditioning
  - HSCT 11 days after kidney transplantation



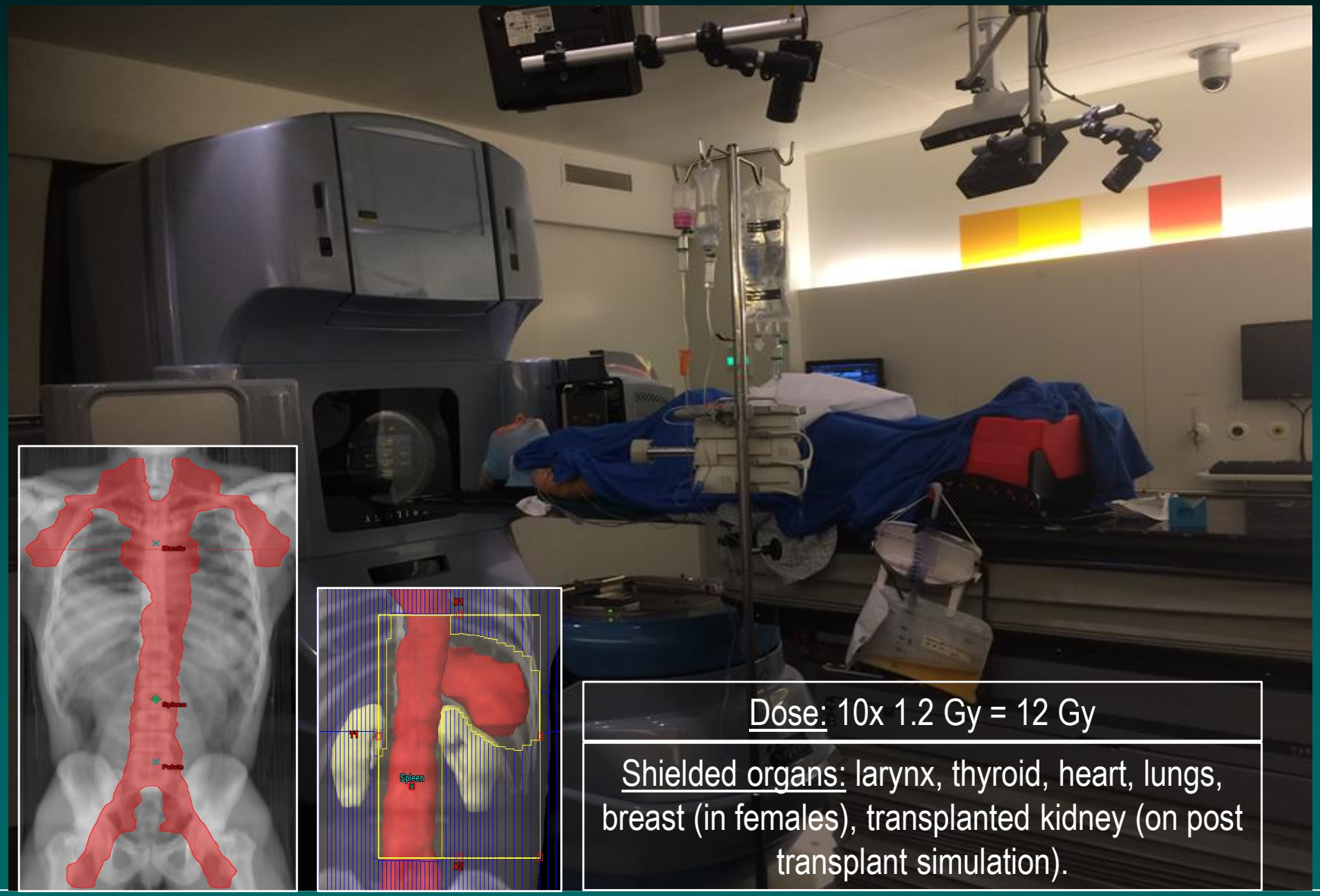
Fehr, Front Immunol 2022

Our first patient – transplantet on Nov 8th 2016

- **57y old female social worker**
- **Kidney disease: sclerosing GN**
  - Kidney biopsy 06/2012: Mainly sclerosing glomerulonephritis, no further specification possible
- **Comorbidities**
  - M. Menière

- **Donor: her healthy HLA-identical brother**

Patient 1 – Total lymphoid irradiation 8.11. - 18.11.2016



Dose: 10x 1.2 Gy = 12 Gy

Shielded organs: larynx, thyroid, heart, lungs, breast (in females), transplanted kidney (on post transplant simulation).

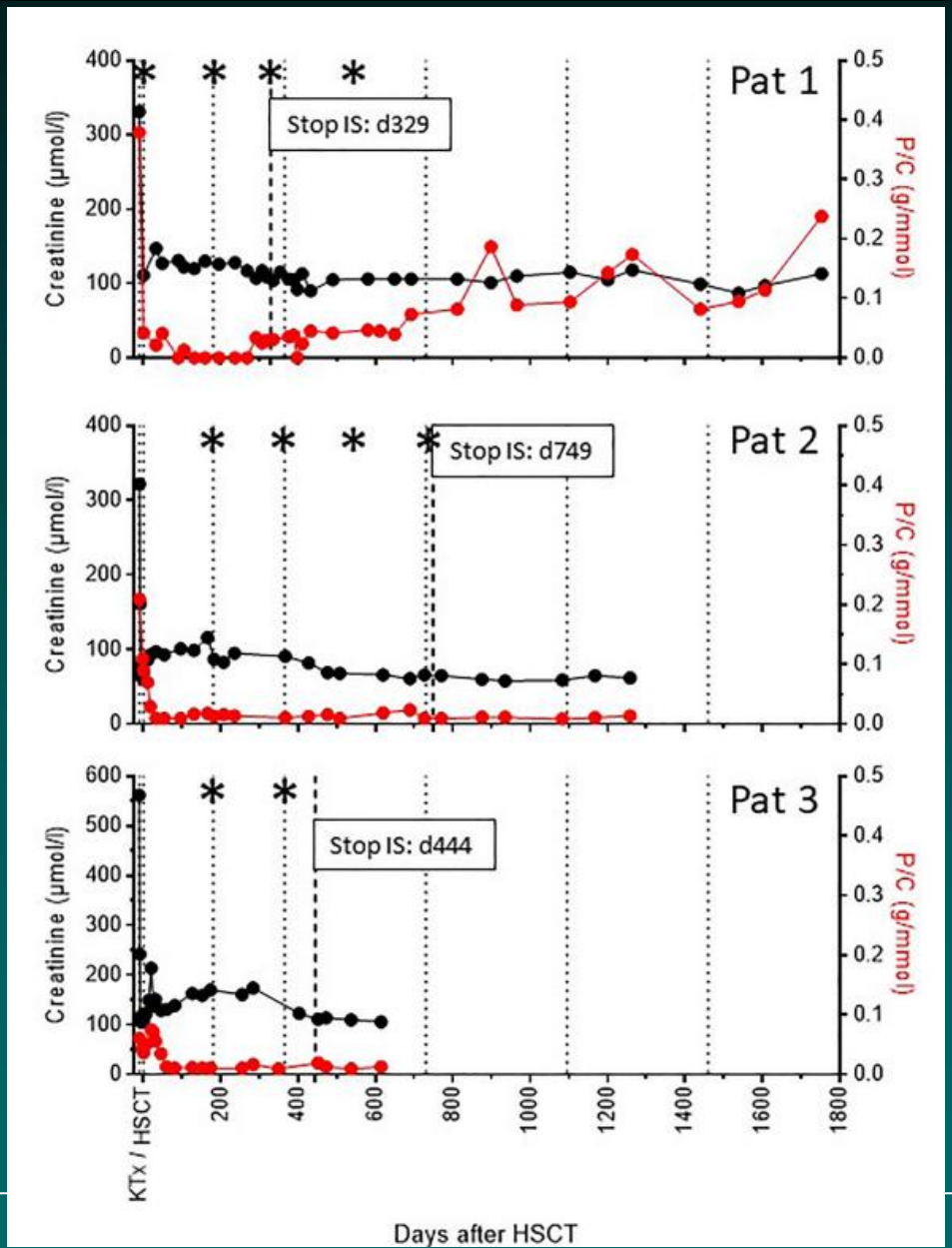
Patient 1 – Early course uneventful

- Hospital discharge on day 7

- HSCT on day 11

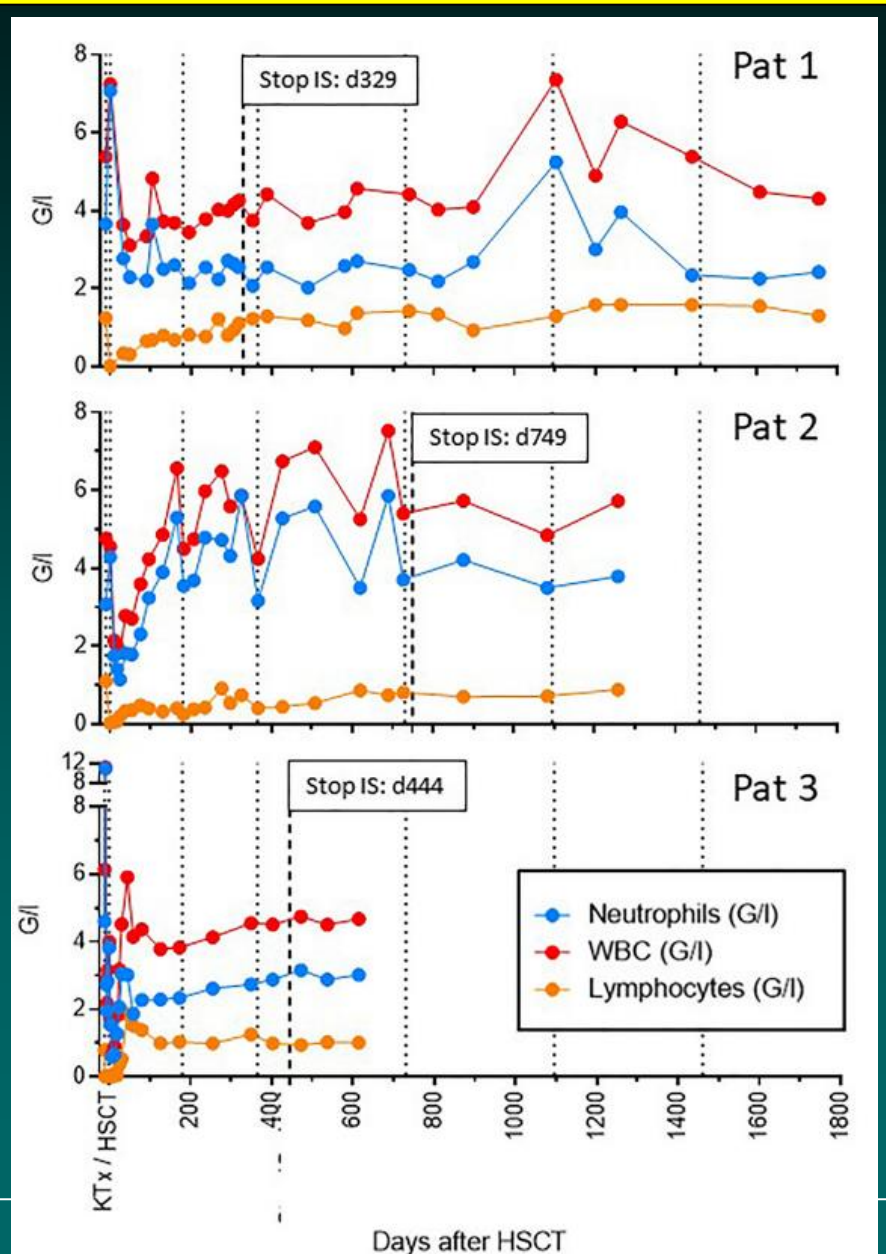
Patient 1-3 – Renal function

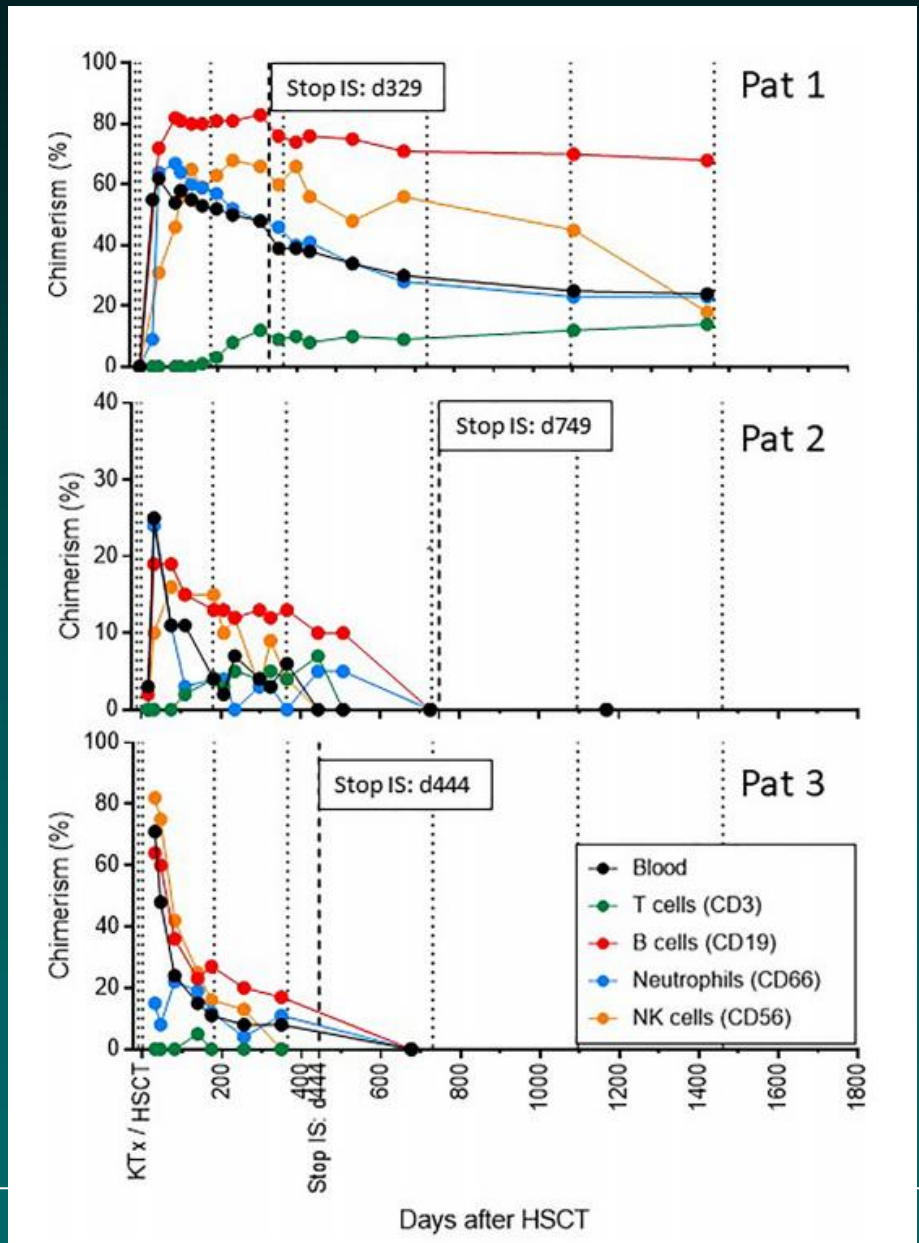
- No rejection episodes
- Recurrence of primary GN in patient 1 – proteinuria



Patient 1-3 – Hematology & chimerism

- **No severe neutropenia**
- **Chimerism**
  - Stable mixed in patient 1
  - Transient in patient 2 & 3





Overview results of 6 patients

- **Screening: 13 HLA-identical pairs**
  - 7 screening failures: ABO incompatibility, medical contraindication for donation
  - 6 pairs included (4 from ZH, 2 from BE)

Pat	Sex	Renal disease	Tx	Stop IS	Off IS	Chimerism	Rejection	GvHD	Recurrent disease
01	F	Sclerosing GN	11/2016	10/2017	**> 6.5 y**	Mixed – stable	No	No	Yes
02	F	Undefined GN	02/2018	03/2020	**> 4.5 y**	Mixed – transient	No	No	No
03	M	ADPKD	11/2019	02/2021	**> 3.5 y**	Mixed – transient	No	No	No
04	M	IgA	07/2021	07/2022	**> 2 y**	Mixed – transient	No	No	No
05	F	ADTKD	06/2021	09/2022	**24 mts**	Mixed – transient	No	No	No
06	M	Vascular	07/2022	06/2023	**15 mts**	Mixed – stable	No	No	No

Is it donor-specific tolerance?

swiss tolerance.CH

- **Acceptance of an allograft without immunosuppression**
- **Evidence:**
  - No rejection
  - No graft-versus-host disease
  - Molecular microscope

- **Full immunocompetence towards infectious agents or vaccines**
- **Evidence**
  - No severe infections (mild CMV & BK viremia)
  - SARS CoV2 vaccination

Patient 2 – Molecular microscope at 18 months

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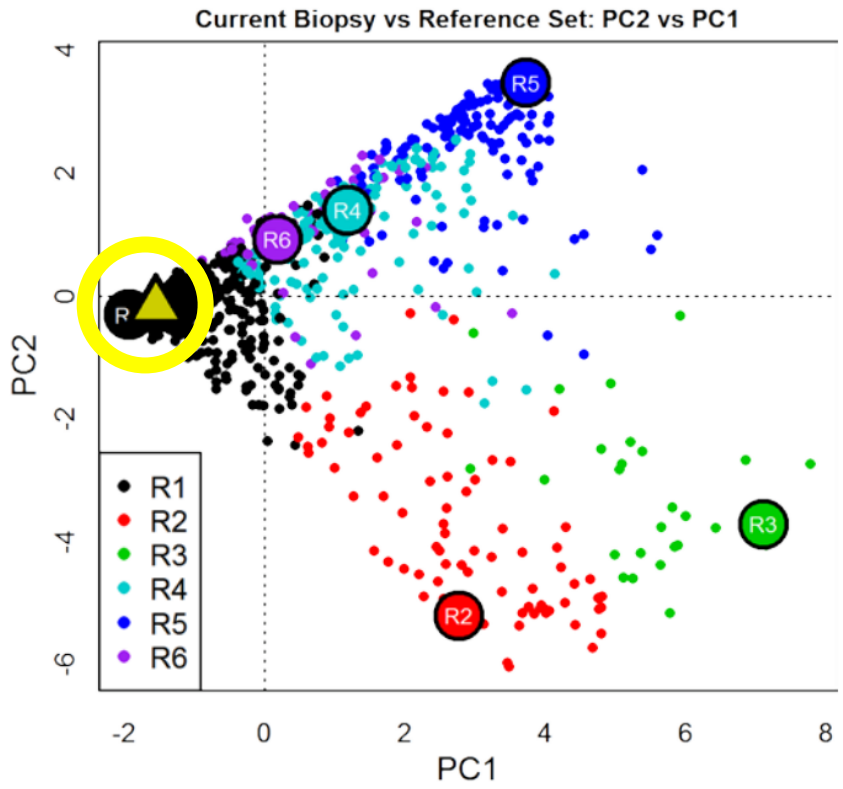
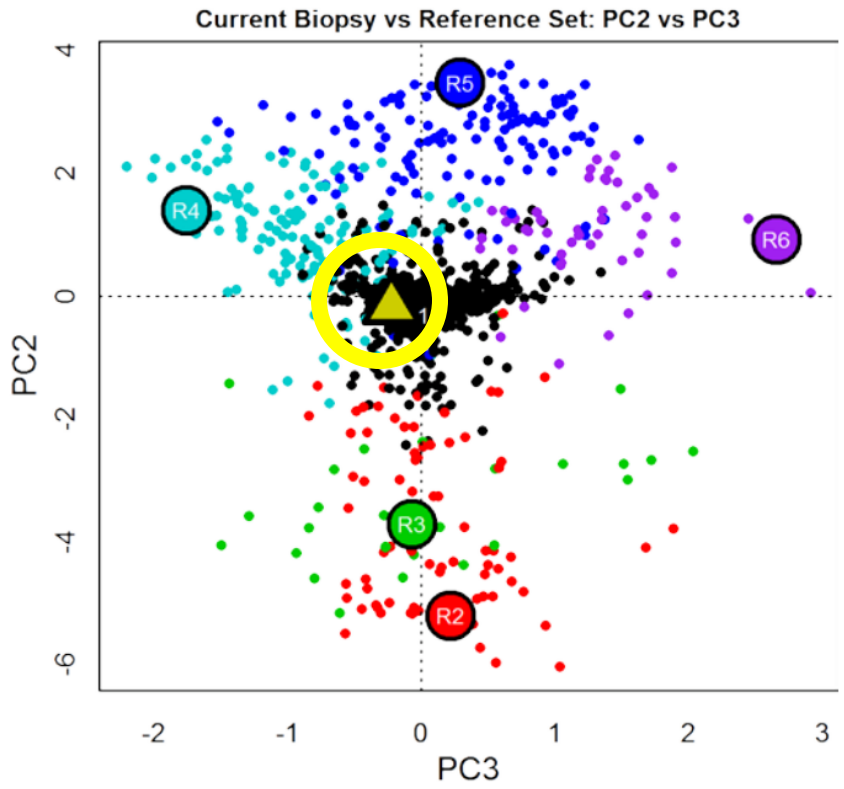
- mRNA microarray of around 60 genes for molecular diagnosis

Rejection phenotype[9, D] (six scores, R1-R6, adding up to 1.0)	R1 Non-rejecting	0.90	All ABMR (Sum of R4, R5, and R6)	0.09
	R2 TCMR	0.00	*R4 Early-Stage ABMR (EABMR)*	0.08
	R3 Mixed Rejection	0.01	*R5 Fully-Developed ABMR (FABMR)*	0.00
			R6 Late-Stage ABMR (LABMR)	0.00





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Patient 1-3 – Immunocompetence for vaccination

- **Successful SARS CoV2 vaccination in all three patients**

Patient No		Patient 1	Patient 2	Patient 3
Vaccination	Vaccine	Cominarty ®	Cominarty ®	Cominarty ®
	1st vaccination	29.1.2021	29.4.2021	14.1.2021
	2nd vaccination	5.3.2021	18.5.2021	11.2.2021
SARS CoV2-specific antibody response	Elecsys ® (Roche), anti-NP IgG (<1.0)	Not reactive, 0.074	Not reactive, 0.076	Not reactive, 0.075
	Elecsys ® (Roche), anti-Spike IgG (<0.8)	Positive, 1488 U/ml	Positive, 1951 U/ml	Positive, 919 U/ml
	Abacor ® (IMV), neutralization score (protective score > 17)	Protective, 28.2	Protective, 83.9	Protective, 40.3
SARS CoV2-specific T-cell response (net stimulation, % CD3+)	Concanavalin A	46.7%	55.2%	63%
	St. aureus superantigen	66.9%	67.7%	71%
	CMV antigen	(17%) *	(10%) *	76%
	SARS CoV2 SP subunit 1	0	27.1%	5%
	SARS CoV2 SP subunit 1	1.1%	14.5%	6%

Fehr, Front Immunol 2022

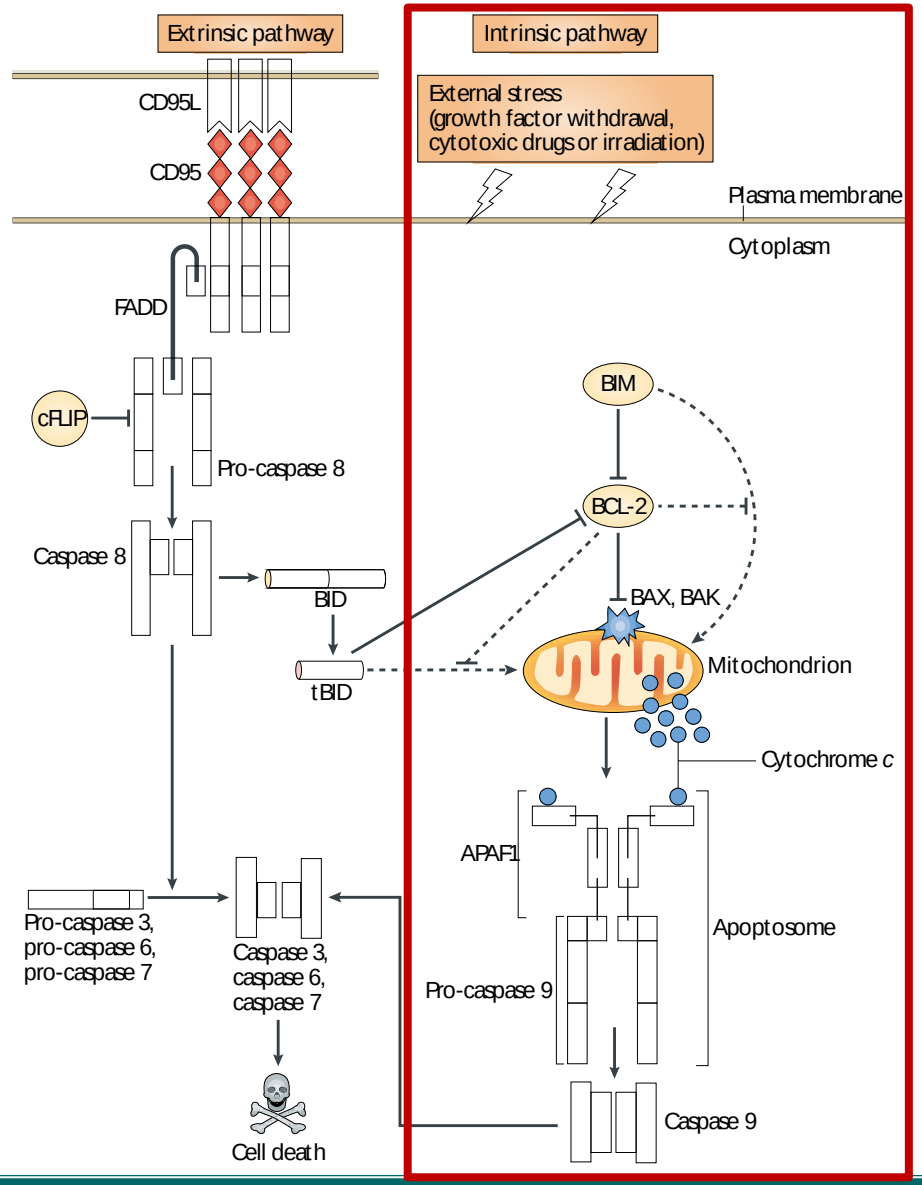
Topics

- **Part I – General background on mixed chimerism and tolerance**
- **Part II – Swisstolerance.CH trial**
- **Part III – Future directions**
  - HLA-identical transplants – planned further research
  - HLA-mismatched transplants – Bcl-2 inhibitor-based approach

HLA-mismatched transplants – new approaches required!

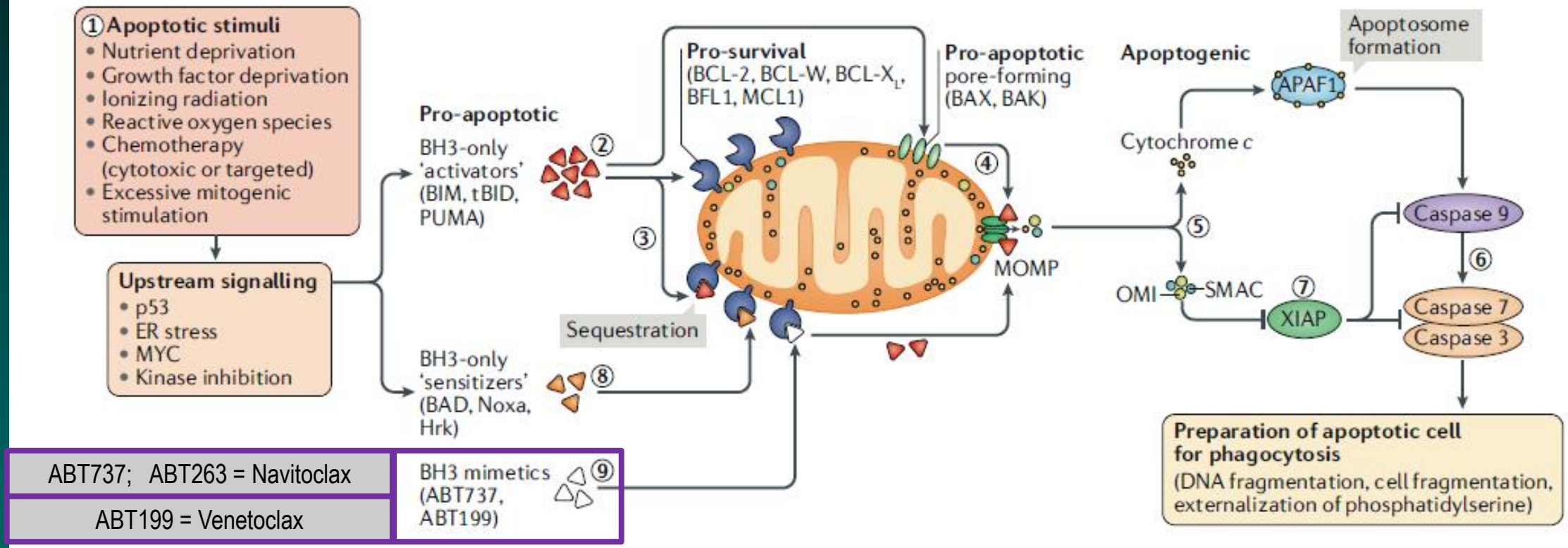
- **Approach evaluated by the Zurich group:** ***apoptosis modulation***

Apoptosis plays a critical role in the adaptive immune system:
- during thymic positive & negative selection
- during peripheral deletion
- during the contraction phase of the immune response



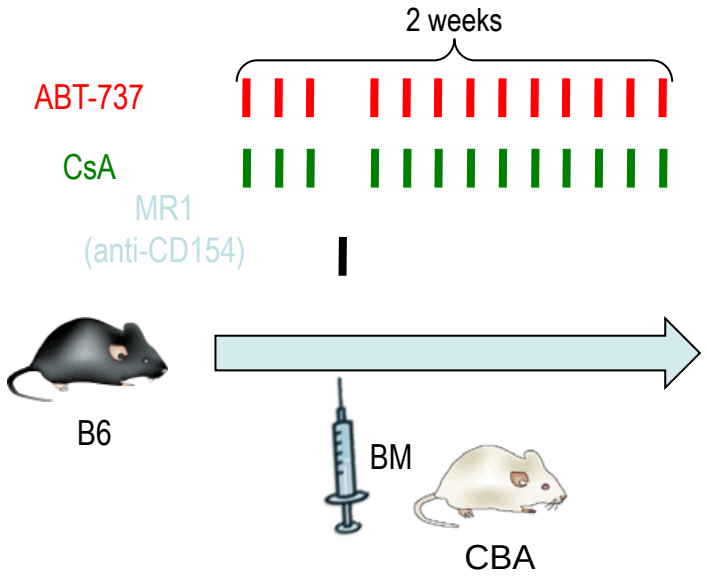
Bouillet, *Nat Rev Immunol* 2009

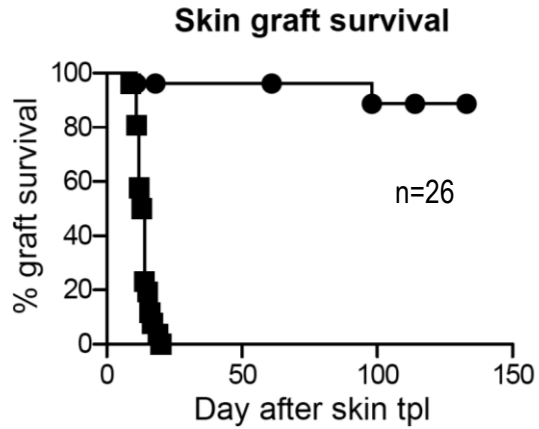
Bcl-2 inhibitors: mechanism of action



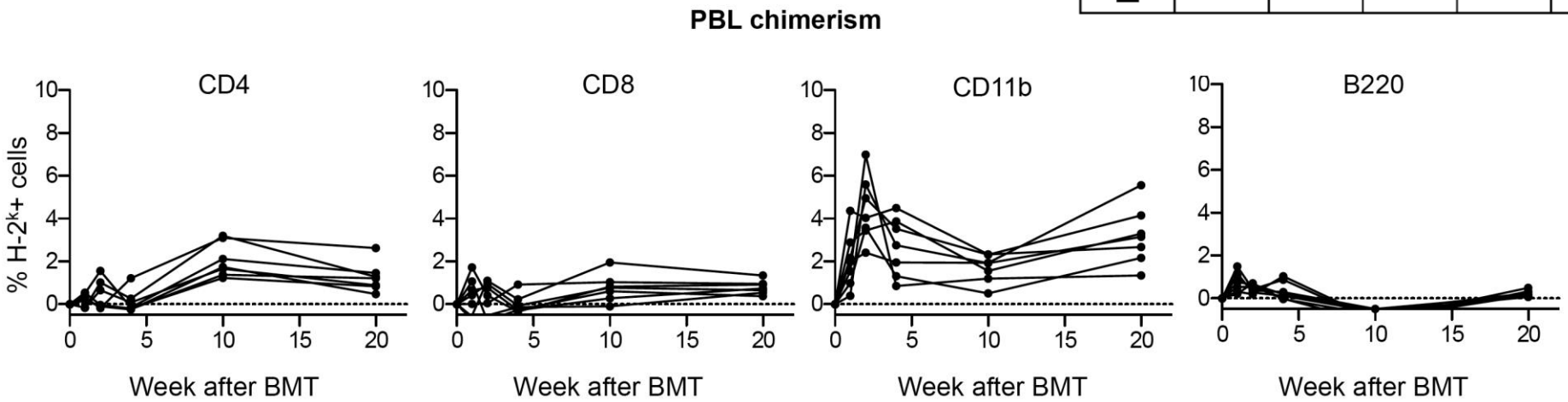
Singh, Nat Rev / Mol Cell Biology 2019

Murine model of mixed chimerism: tolerance induction without myelosuppression





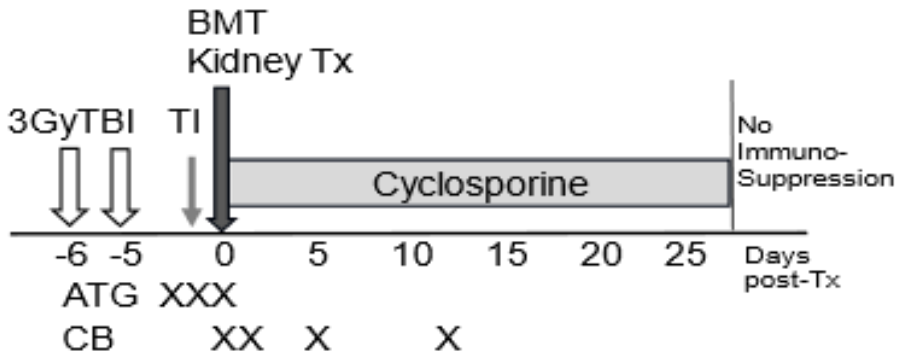
	TBI	BM	ABT	CsA	CSB	Skin
●	-	CBA	+	+	MR1	CBA
■						Balb/c



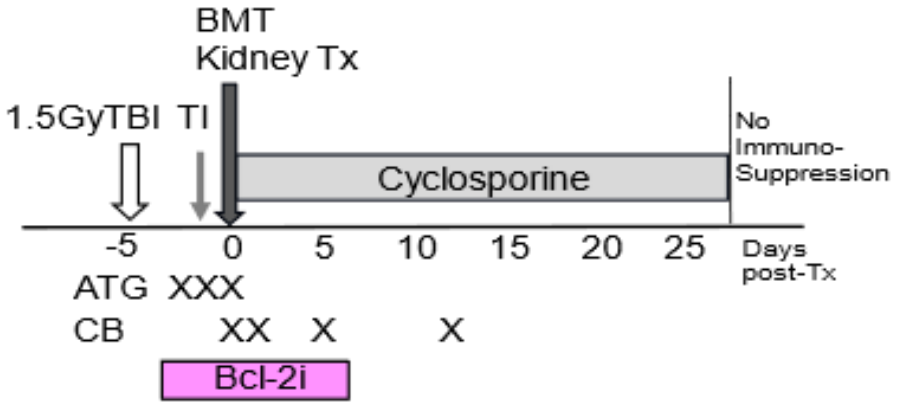
Cippà, *Blood* 2013

Non-human primate model of mixed chimerism: protocol

Previous Protocol

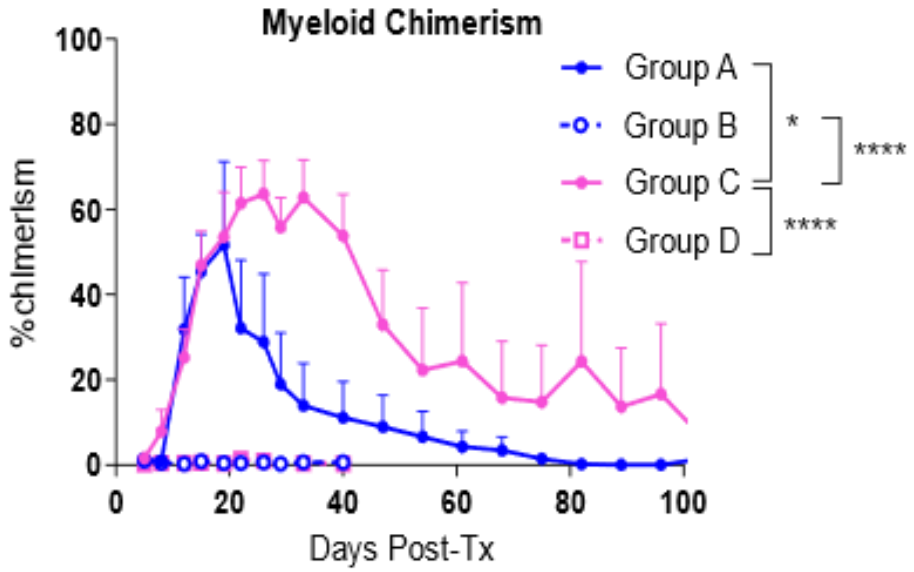


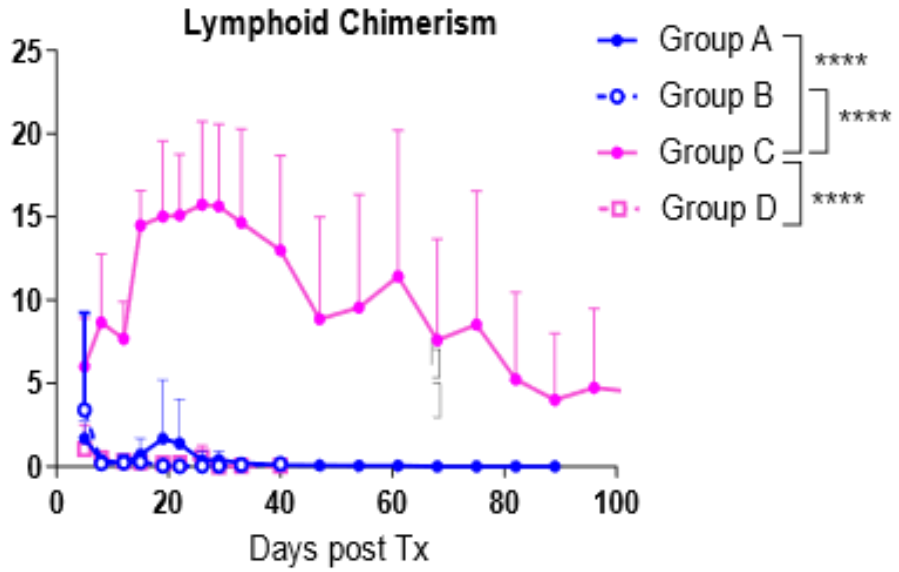
Bcl-2i Protocol

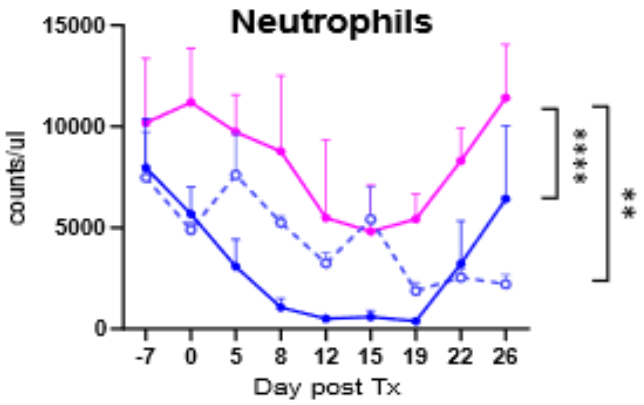


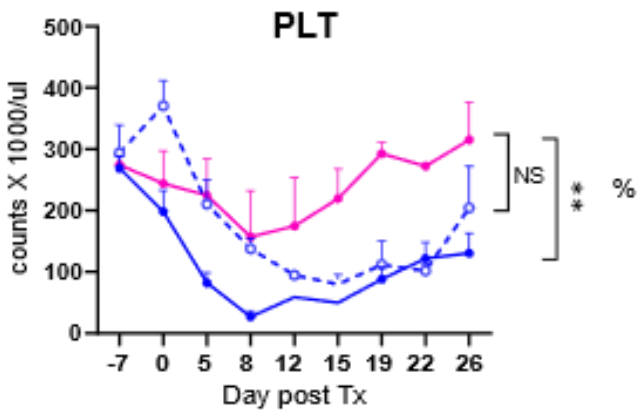
Group A (n=8) TBI 3Gy, no Bcl-2i
Group B (n=5) TBI 1.5Gy, no Bcl-2i
Group C (n=6) TBI 1.5Gy, +Bcl-2i
Group C (N=2) TBI 0 Gy, + Bcl-2i

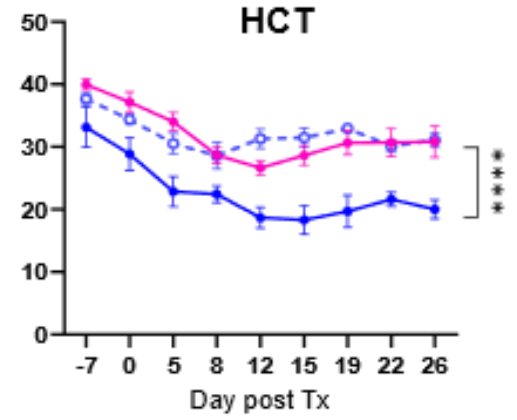
Non-human primate model of mixed chimerism: chimerism





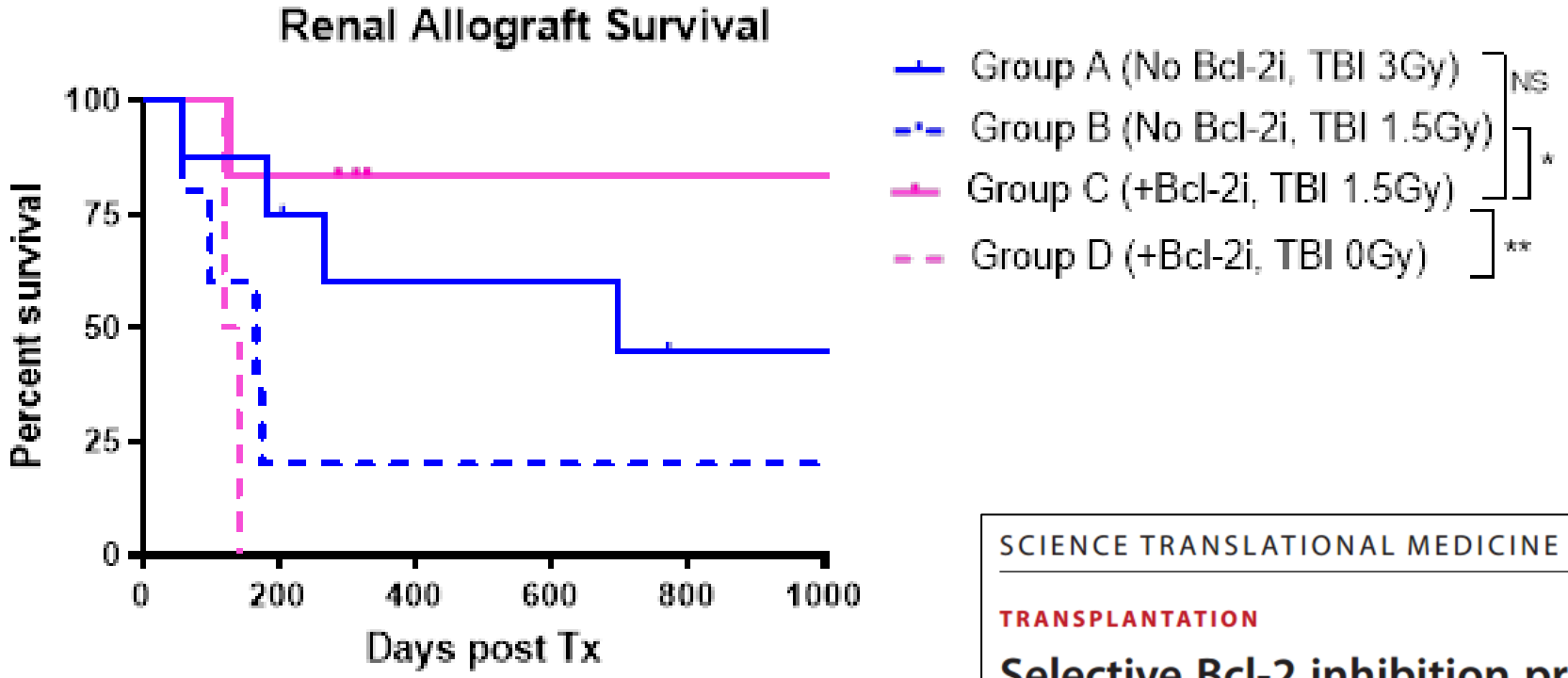






Sasaki / Fehr / Kawai, Science Translational Medicine 2023

Non-human primate model of mixed chimerism: renal allograft survival



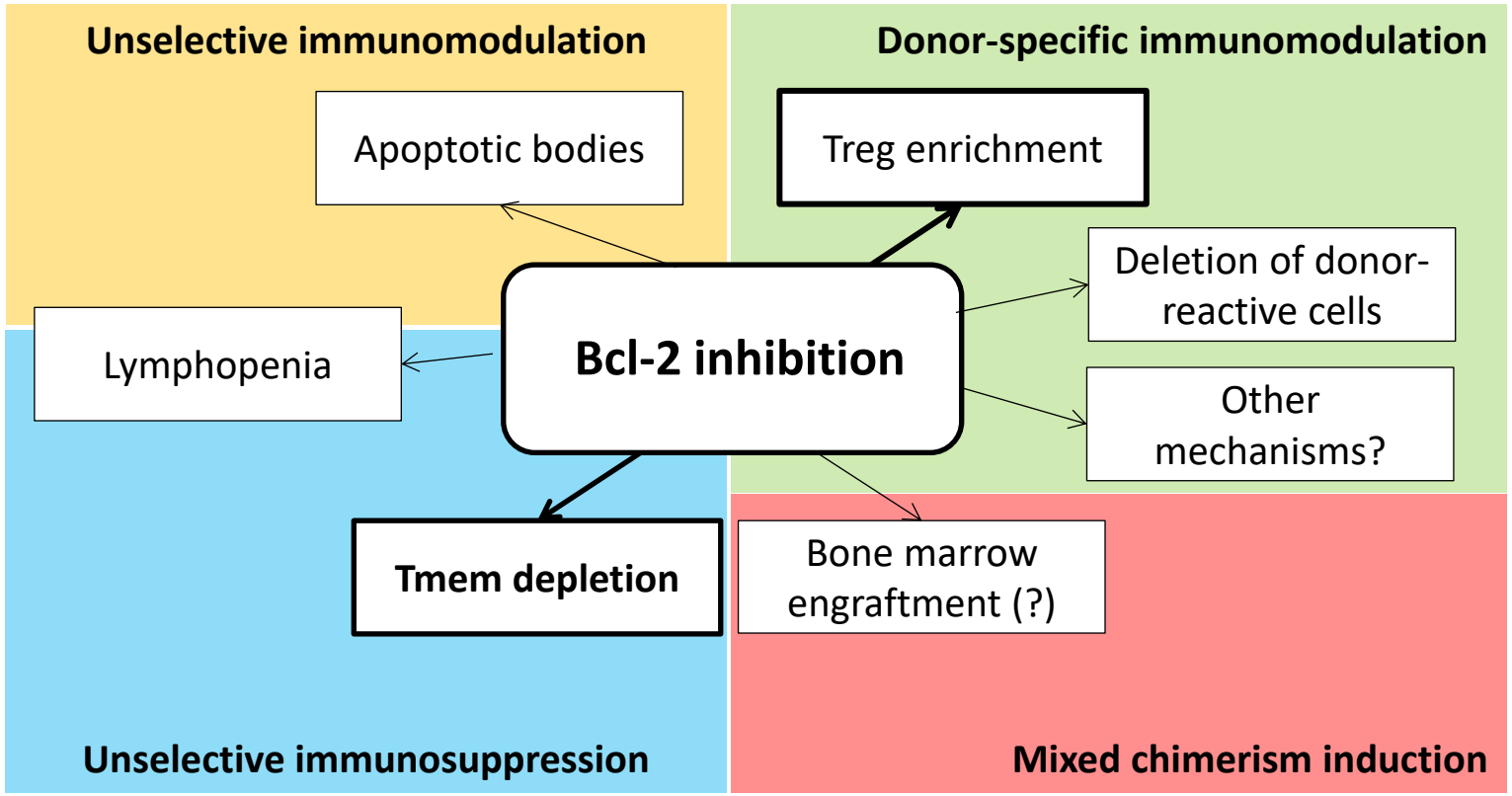
SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

TRANSPLANTATION

Selective Bcl-2 inhibition promotes hematopoietic chimerism and allograft tolerance without myelosuppression in nonhuman primates

Hajime Sasaki[1†], Takayuki Hirose[1†], Tetsu Oura[1], Ryo Otsuka[1], Ivy Rosales[2], David Ma[1], Grace Lassiter[1], Ahmad Karadagi[1], Toshihide Tomosugi[1], Abbas Dehnadi[1], Masatoshi Matsunami[1], Susan Raju Paul[3], Patrick M. Reeves[3], Isabel Hanekamp[1], Samuel Schwartz[1], Robert B. Colvin[2], Hang Lee[4], Thomas R. Spitzer[3], A. Benedict Cosimi[1], Pietro E. Cippà[5], Thomas Fehr[6,7], Tatsuo Kawai[1*]

Multiple immunomodulatory effects of Bcl-2 inhibition



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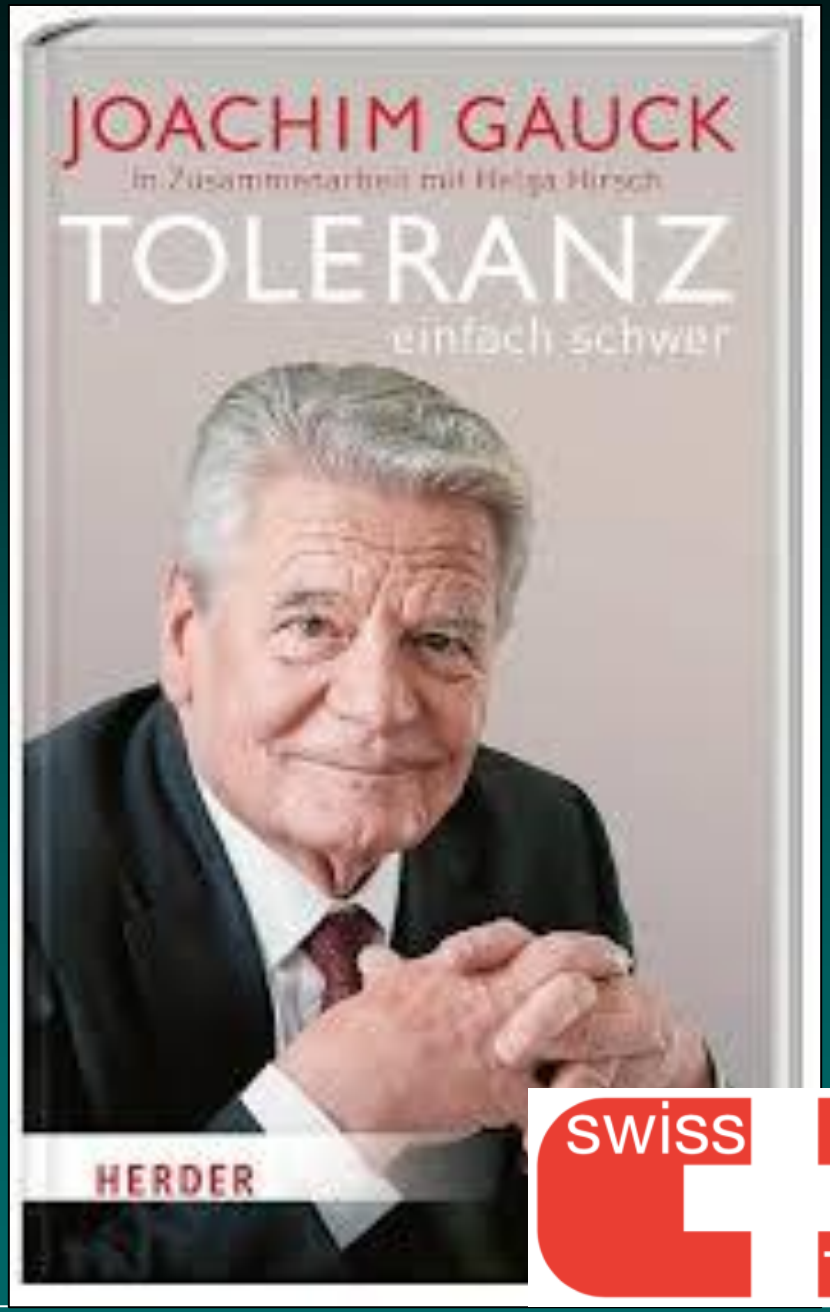

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FACT OR FICTION ?

Voltaire

Über die Toleranz

Suhrkamp