



**Graft-versus-GVHD, a second transplantation from another donor for the rescue from refractory acute GVHD**



## **The Hospital of Hyogo College of Medicine**

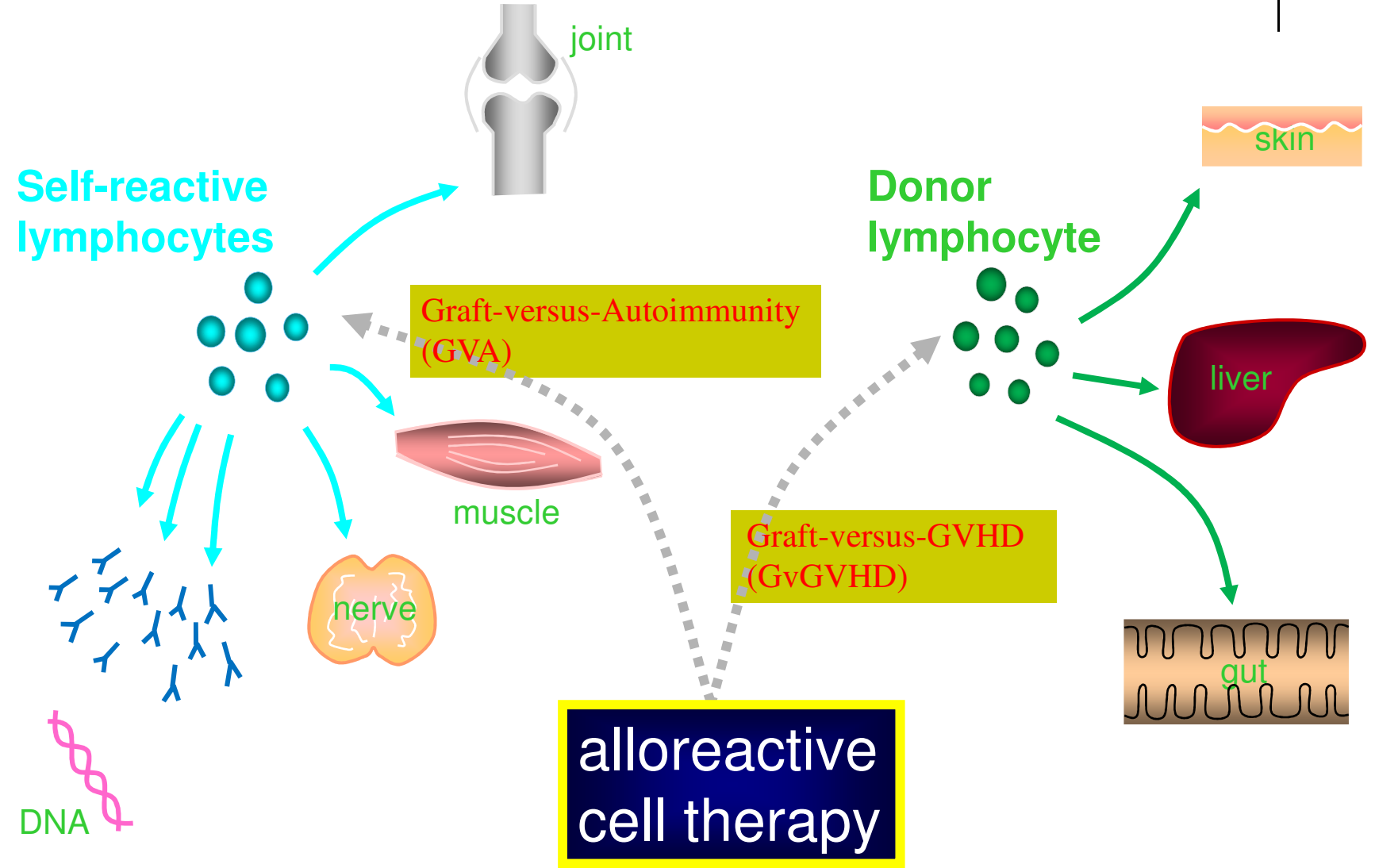
**Hyogo College of Medicine Kazuhiro Ikegame**

# Concept of Graft-versus-GVHD (GvGVHD)

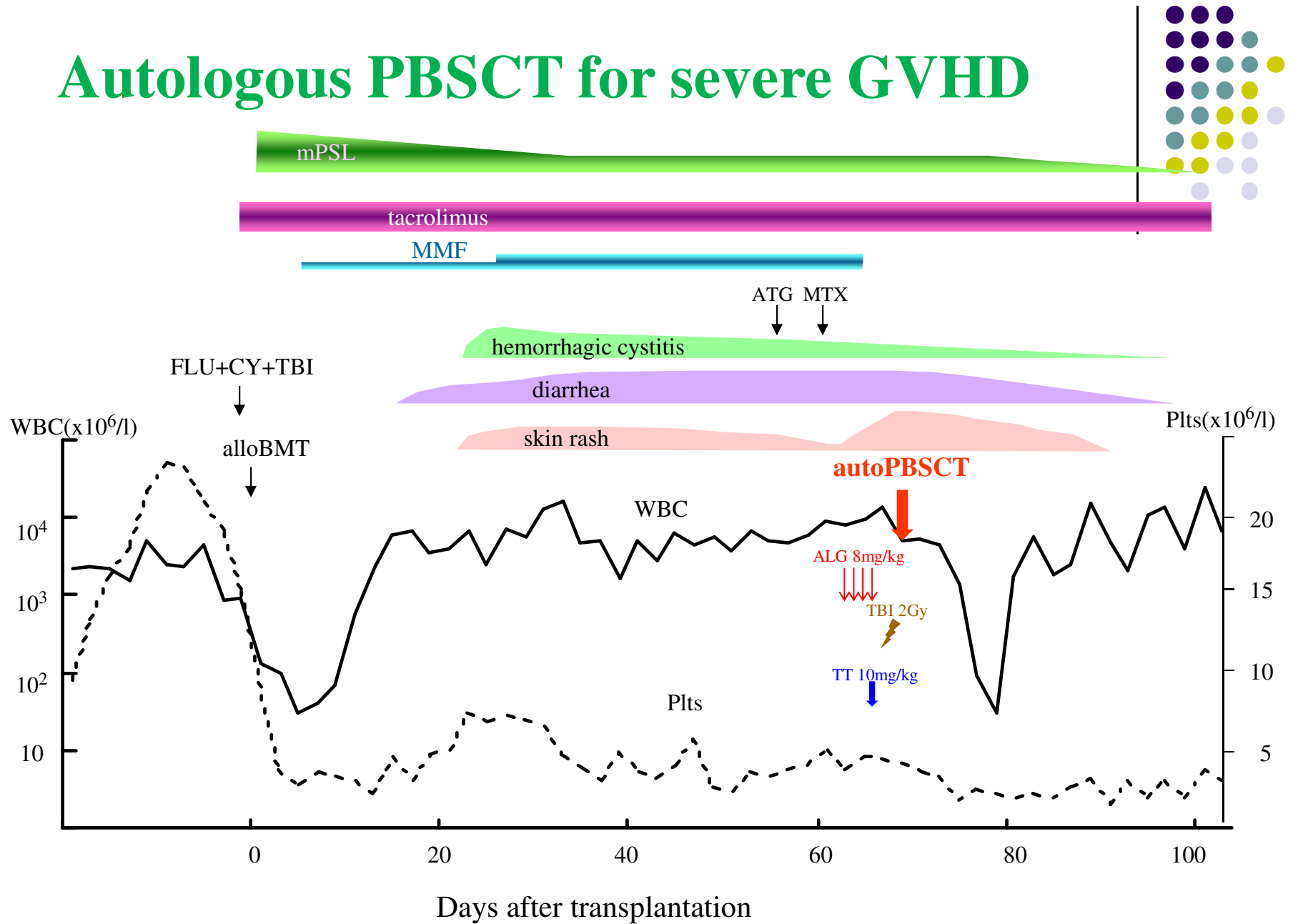


## Autoimmune

## GVHD



# Autologous PBSCT for severe GVHD



BM relapse on day 144 after 2<sup>nd</sup> autoPBSCT

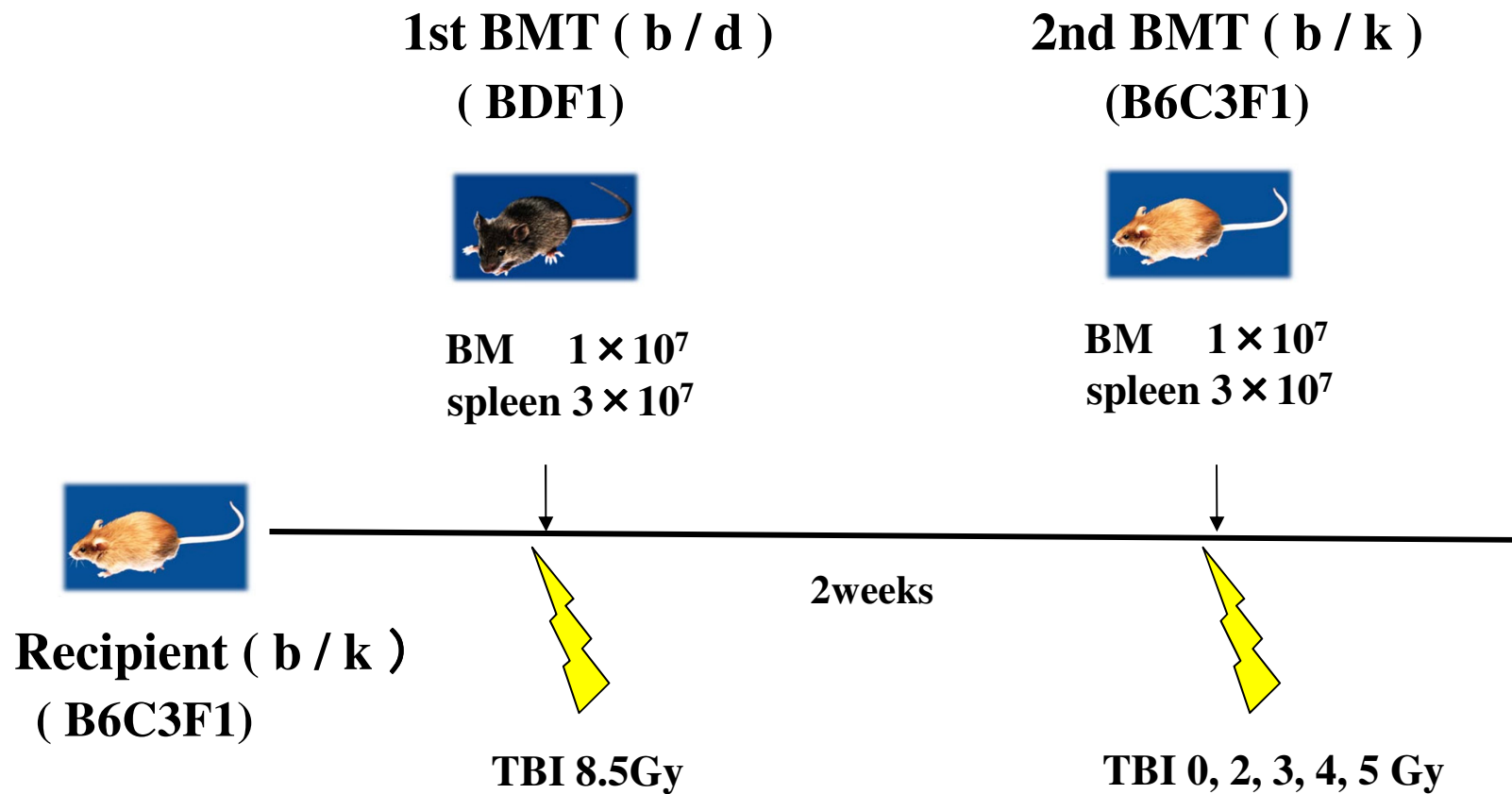
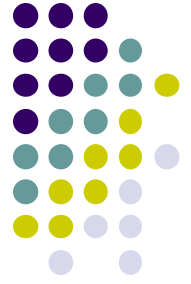
# Case reports of autologous PBSCT for GVHD

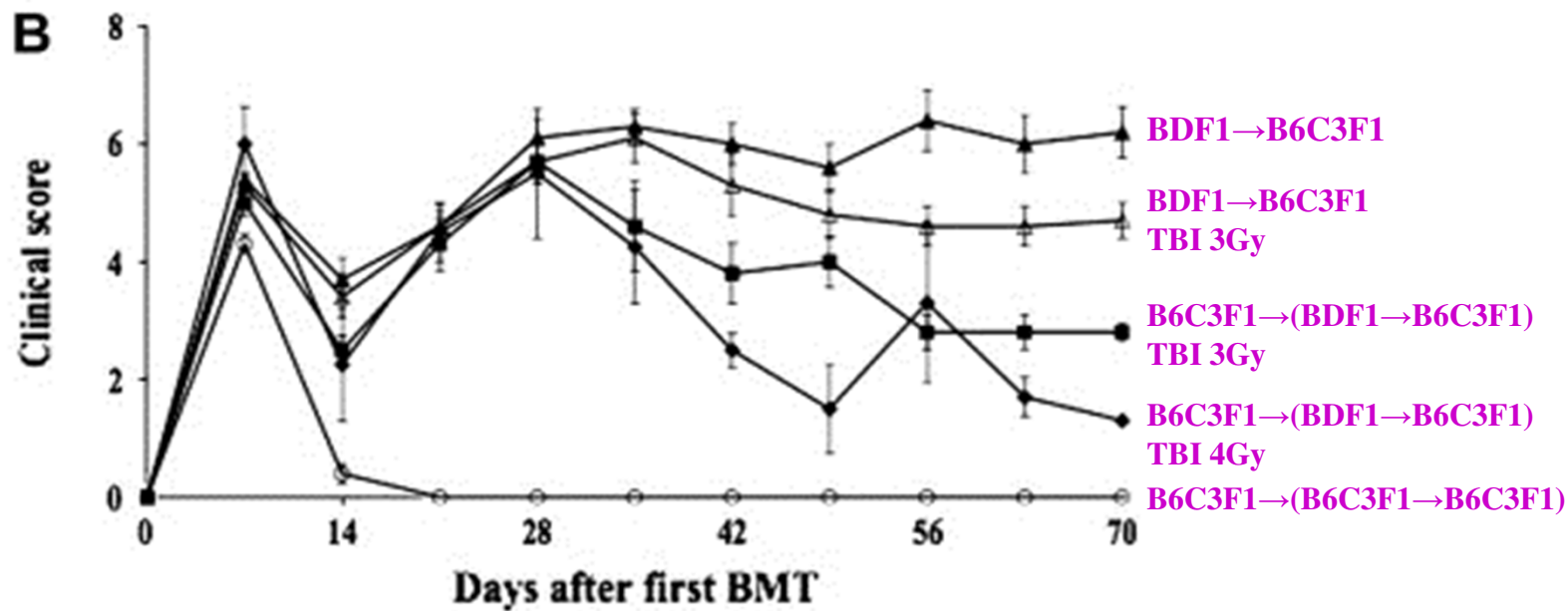
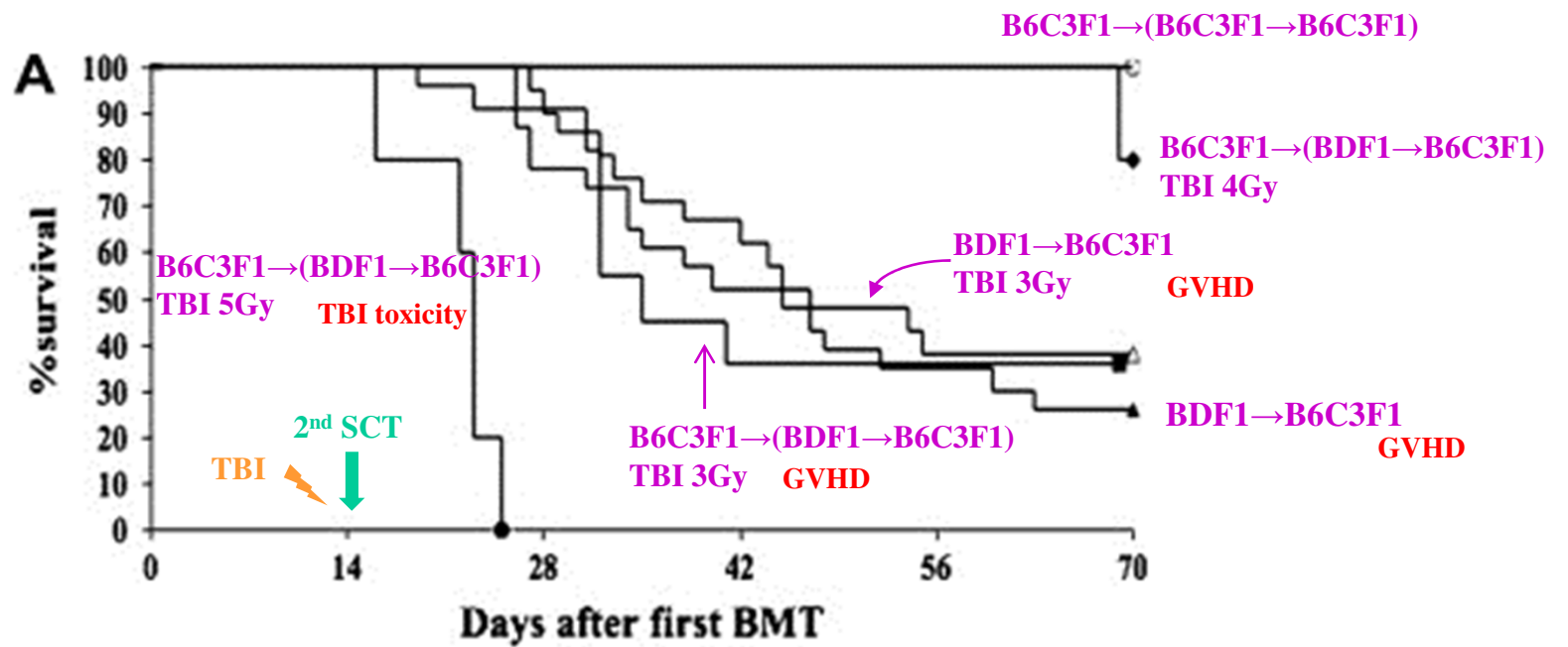


Patient	Time to BMT2 (days)	SC source	Donor SCT2	Cell dose/kg	Conditioning SCT2	Immunosuppression	Chimerism post-SCT2	Outcome of GvHD	Alive	Time (days)	COD
1	270	PB	Id twin	$5.2 \times 10^8$ CD34	Fludara/2GyTBI	CsA, steroids	Patient 100%, mixed in BAL	Minor improvement, transient	Dead	70	GvHD
2	45	PB	Auto	$4.5 \times 10^8$ CD34	Fludara/2GyTBI	CsA, steroids	Mixed	Minor improvement, transient	Dead	35	GvHD
3	56	BM	Auto	$3.6 \times 10^8$ CD34	None	CsA, steroids	Donor 100%	aGvHD completely resolved, limited cGvHD at 7.5 months	Dead	730	Relapse
4	91	BM	Id twin	$2.9 \times 10^8$ NC	Bu 16 mg/kg	CsA, steroids, Campath-1G	Not tested	aGvHD resolved	Dead	112	MOF
5	203	PB	Auto	$6.7 \times 10^8$ CD34	None	CsA, steroids, Daclizumab, Etanercept	Donor 100%	Minor improvement	Dead	27	Fungal infection
6	41	PB	Auto	$10.2 \times 10^8$ CD34	None	MMF, steroids	Donor 100%	Partial improvement, transient, recurrence with steroid taper	Dead	43	GvHD
7	61	PB	Auto	$10 \times 10^8$ NC	Cy/ATG/deoxycoformidin	CsA, steroids	Patient 100%	GvHD resolved	Dead	1825	Relapse
8	66	PB	Auto	$10 \times 10^8$ NC	Cy/ATG	Steroids	Patient 100%	GvHD resolved	Alive	+485	

Bone Marrow Transplantation (2004) 34, 995–998

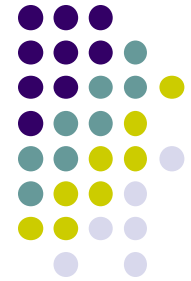
# AutoSCT for GVHD (mouse model)



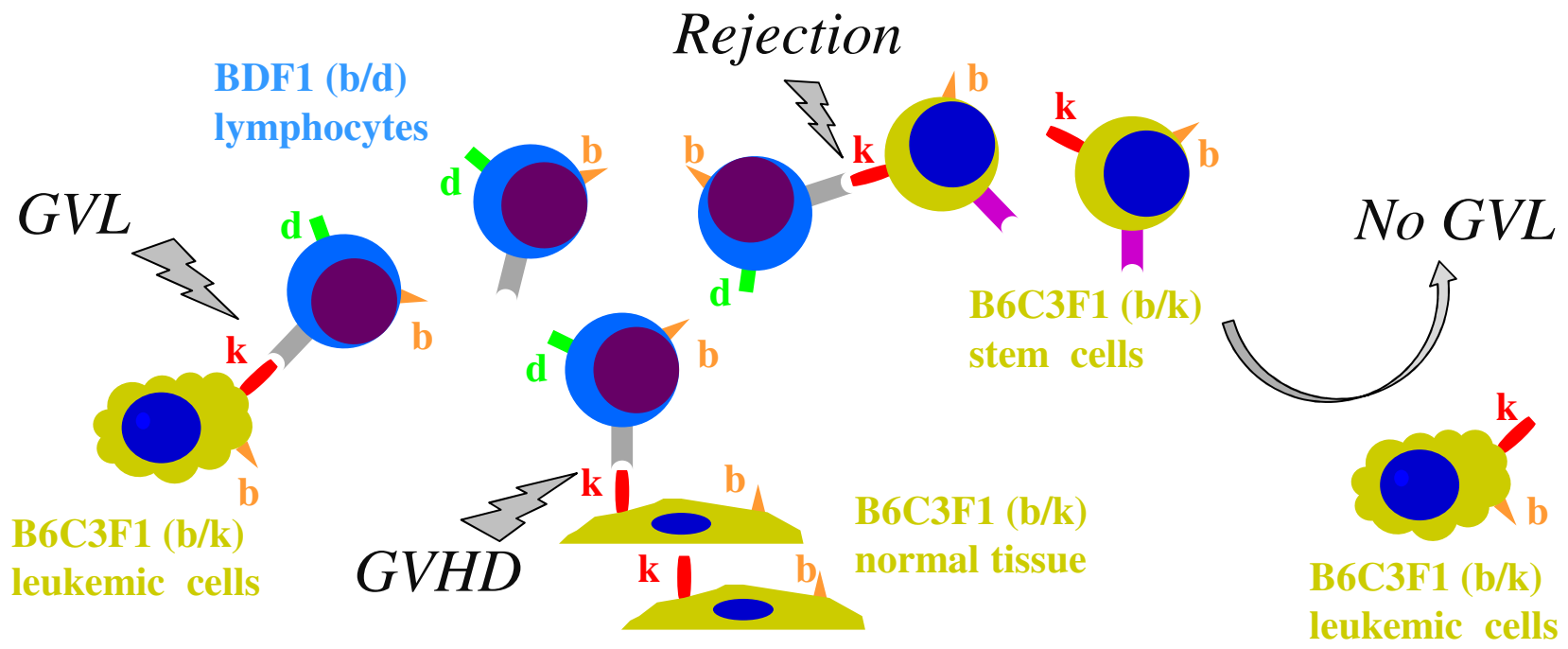




# Problems of AutoSCT for GVHD



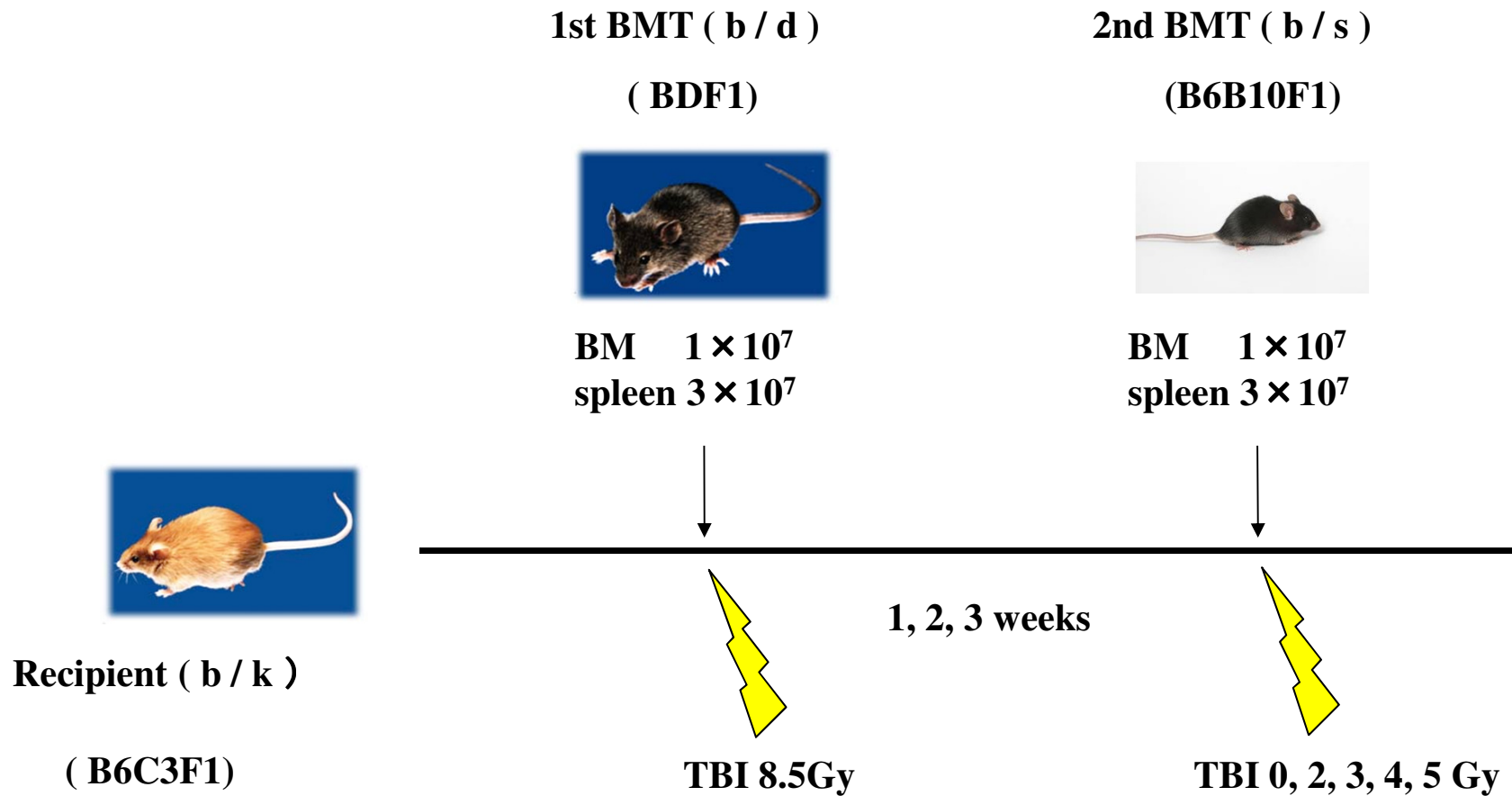
- 1) Difficult to engraft (GVH clones are rejecting clones)
- 2) Risk of relapse (Loss of GVL effect)



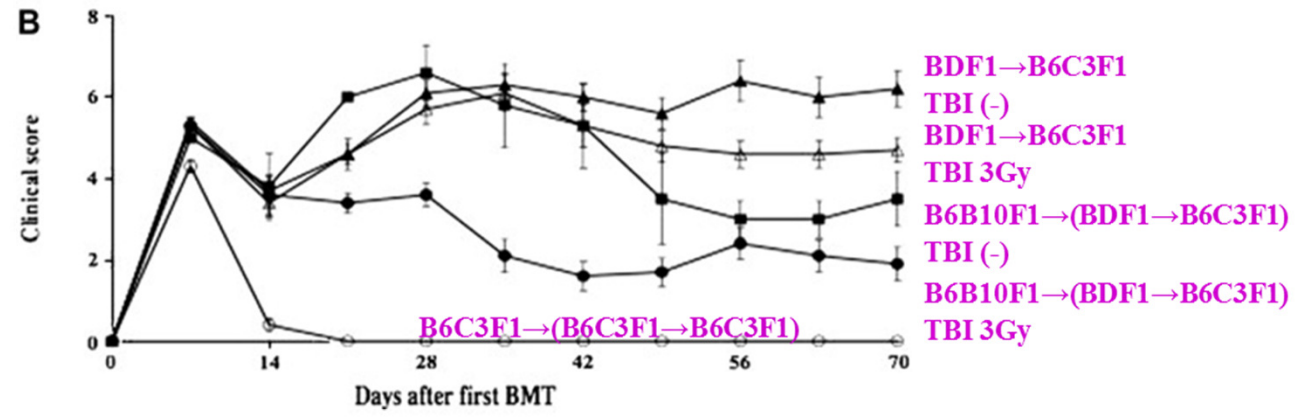
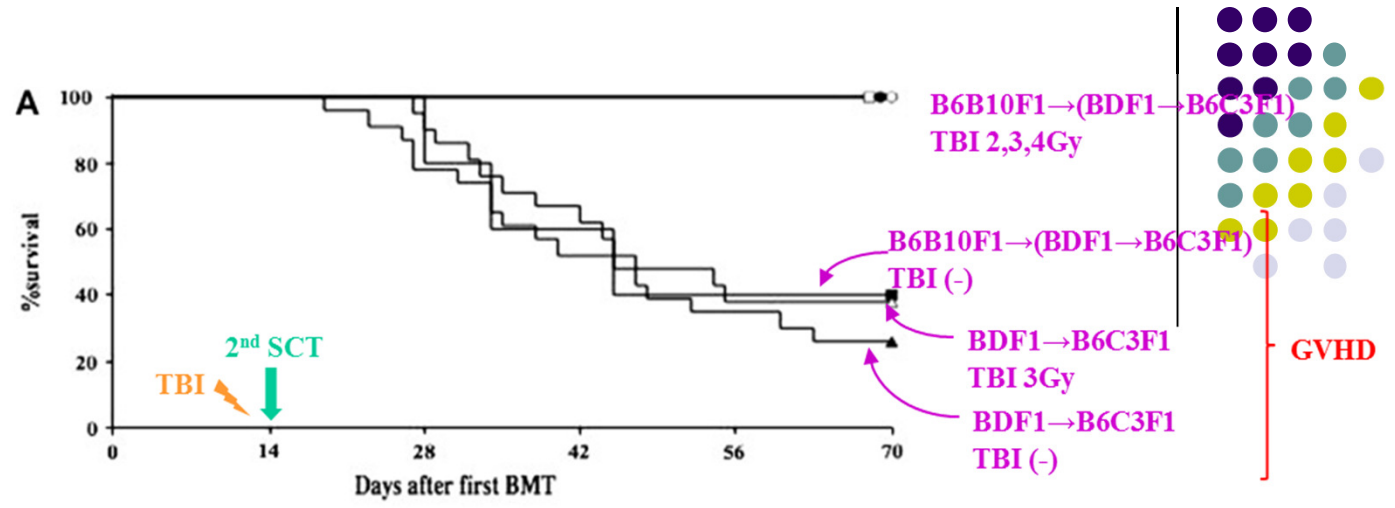




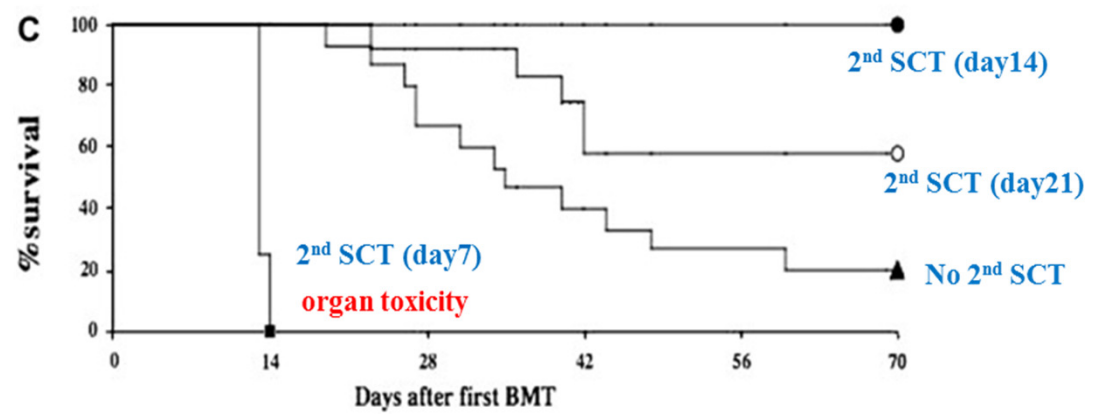
# AlloSCT for GVHD (mouse model)



B6B10F1→(BDF1→B6C3F1)  
 TBI 5Gy  
 All early death due to TBI toxicity



Timing of 2<sup>nd</sup> SCT  
 B6B10F1→(BDF1→B6C3F1)  
 TBI 3Gy



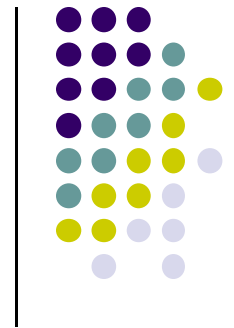
# T cell chimerism of 1<sup>st</sup> and 2<sup>nd</sup> donors after 2<sup>nd</sup> SCT



Experiment	SCT sequence	TBI dose For 2 <sup>nd</sup> SCT	2 <sup>nd</sup> donor chimerism		Improvement in GVHD score
			Day 7	Day 14	
1	B6C3F1 → (BDF1→B6C3F1) b/k            b/d            b/k	3Gy	47 ± 20	95 ± 3.4	±~+
2	B6C3F1 → (BDF1→B6C3F1) b/k            b/d            b/k	4Gy	99 ± 0.8	99 ± 1.1	+
3	B6B10F1 → (BDF1→B6C3F1) b/s            b/d            b/k	3Gy	99 ± 0.9	99 ± 1.1	+
4	B6B10F1 → (BDF1→B6C3F1) b/s            b/d            b/k	0	25 ± 10	18 ± 18	-
5	C3DF1 → (BDF1→B6C3F1) d/k            b/d            b/k	3Gy	2.6 ± 2.5	1.8 ± 3.6	-
6	DBA/2 → (BDF1→B6C3F1) d/d            b/d            b/k	0	40 ± 7.1	25 ± 3.1	-
7	DBA/2 → (BDF1→B6C3F1) d/d            b/d            b/k	3Gy	78 ± 8.6	96 ± 2.5	+

3Gy is not enough when GVHD clones are rejecting clones

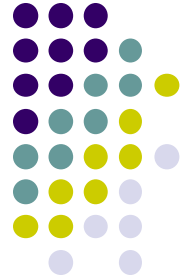
TBI is indispensable in homo-to-hetero (hybrid resistance?)



**Human is more important  
than mouse?**



# Graft-versus-GVHD



## Mouse model

Recovery from established graft-vs-host disease achieved by bone marrow transplantation from a third-party allogeneic donor.

Taniguchi Y, et al. Exp Hematol. 2008.

## Clinical

Allogeneic stem cell transplantation as treatment for heavily treated, refractory acute graft-versus-host disease after HLA-mismatched stem cell transplantation.

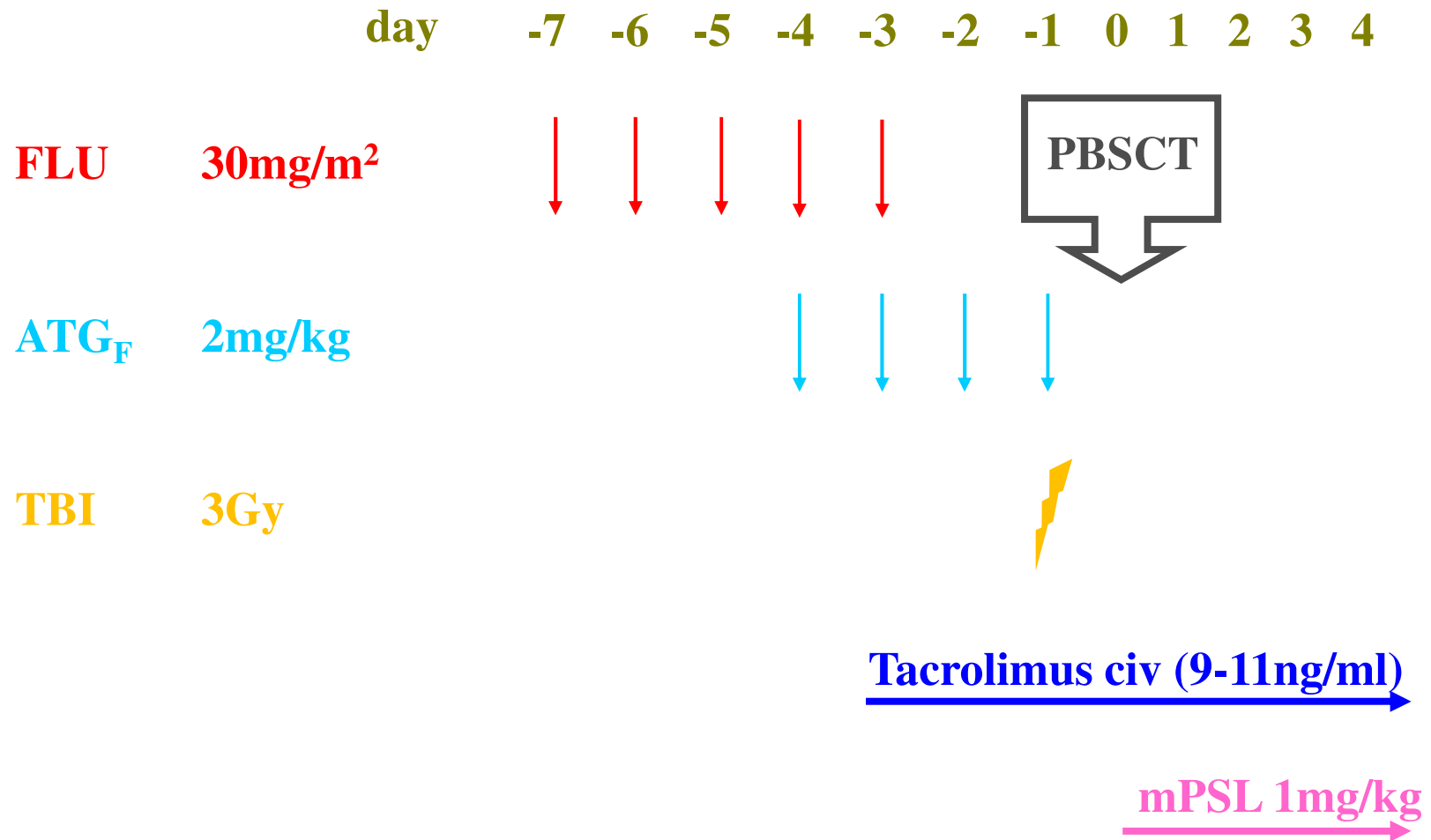
Ikegame K, et al. Exp Hematol. 2011.

**Second SCT for refractory acute GVHD from another haploidentical donor (n=15 cases)**

**Engraftment 11, rejection 4**

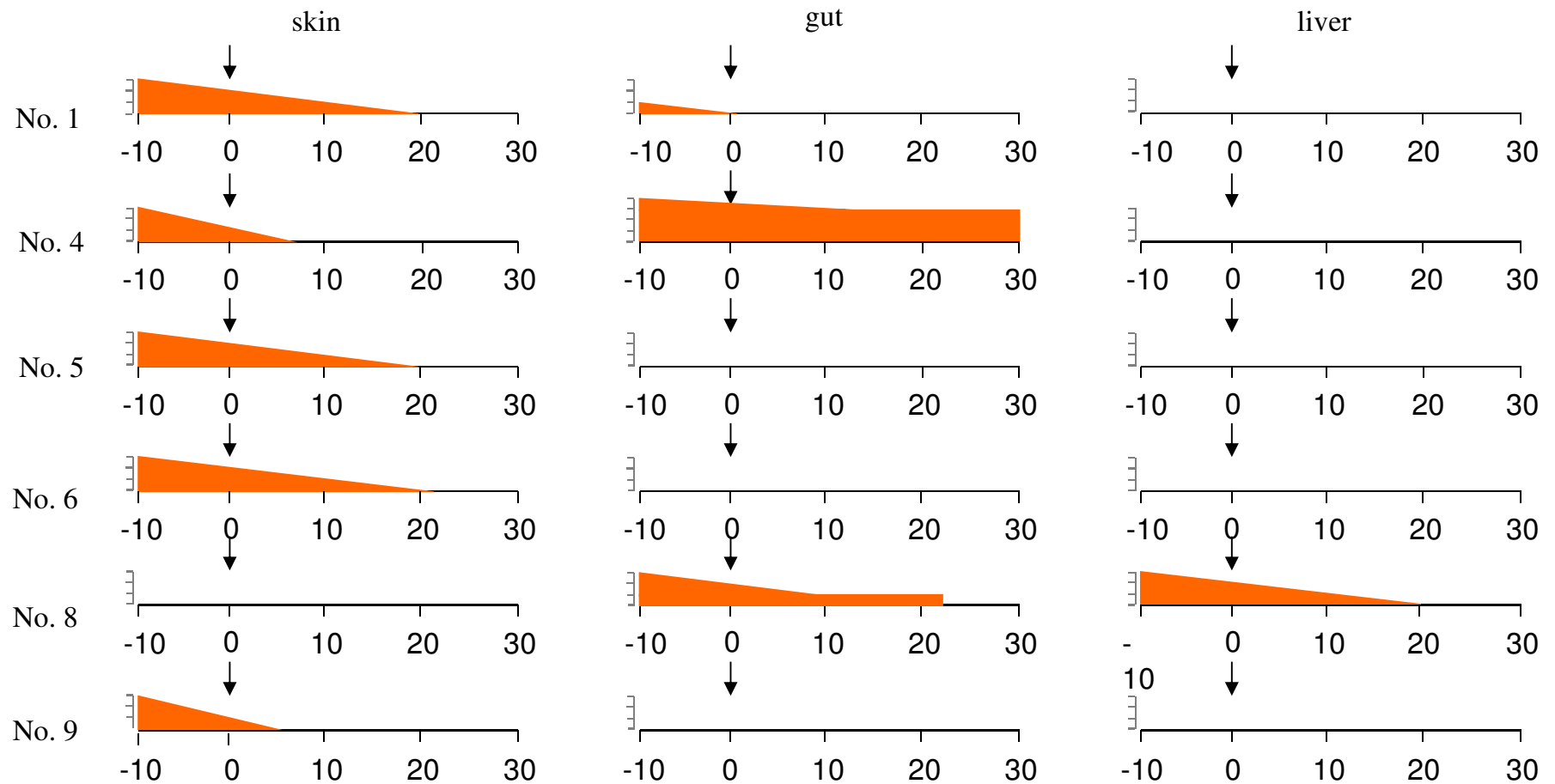
**OS@3yr 53% in engraftment cases, early death of GVHD in all rejected cases**

# Representative regimen of GvGVHD

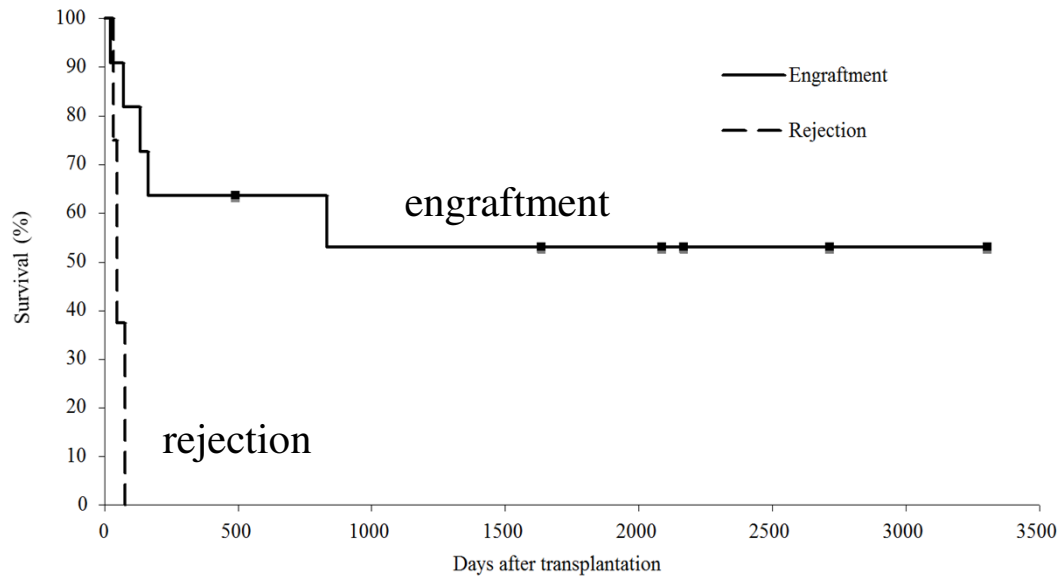
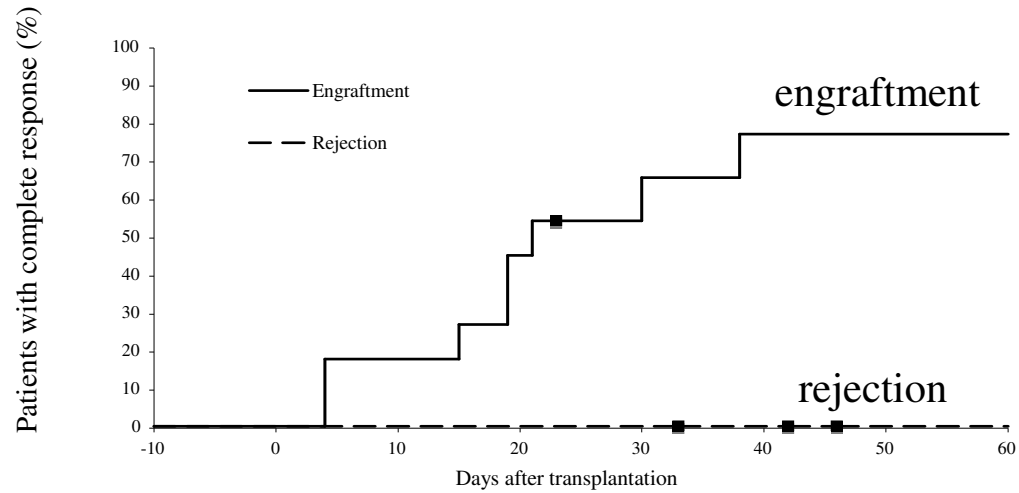




# Change of GVHD stage along time course before and after GvGVHD in engrafted cases

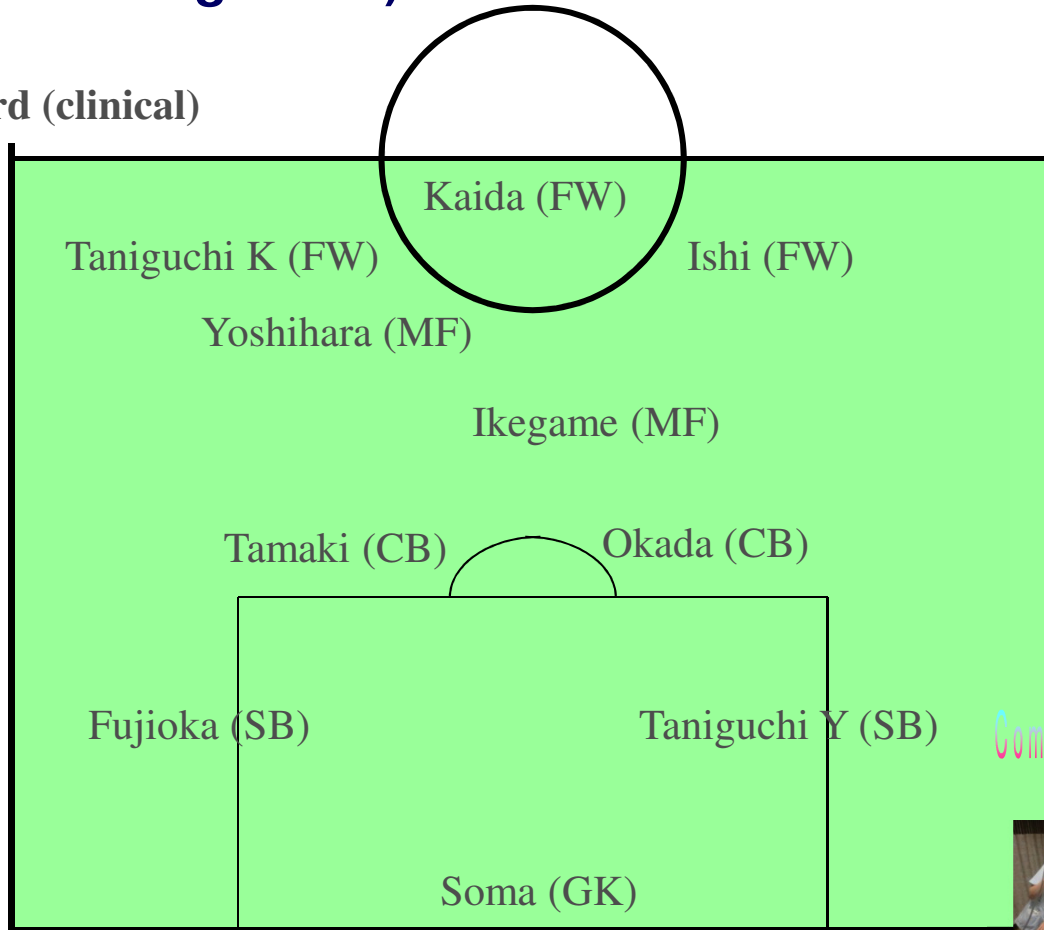


# Response and survival after GvGVHD



# Lineup of HCM (Acknowledgement)

Ward (clinical)



Lab. (research)

(Coach)

Prof. Ogawa



Inoue (graduate student)

Kato (graduate student)

Comedical staffs of the ward

team effort

