“Human Immune System” mouse models for preclinical risk assessment

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European Immunogenicity Platform
27-Feb-2019

Research model creation services at genOway

Rodent & cell models
> 2000 catalog models for target & compound specificity validation
> 2000 tailor-made models
Unique and broad IP platform
Worldwide partnerships (academia & pharmaceutical/biotech companies)

Cytokine-producing cell reporter models

Gene-humanized models with enhanced translatability to human

- PK and PD studies (Hu-FcRn/Hu-albumin)
- IgE mediated inflammation and allergies (Hu-IgE/Hu-FcεR1)
- inflammation & auto-immune disease (Hu-CD4, Hu-TNF-α,…)
- Immune checkpoint and co-stimulatory molecules (OX40, PD-1, GITR,…)

Cell-humanized models for prospective access to human cells in vivo

- Human hematopoietic cells (PBMC, CD34⁺ HSPC,…)
- ± human tumor cells

Construction of “Human Immune System” mice

Human Immune System mice

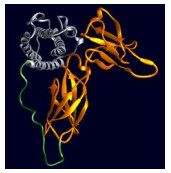
Mice humanized for cellular and molecular components of the hematopoietic system

GENETIC HUMANIZATION

Human DNA

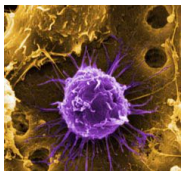
Immuno-deficient mice

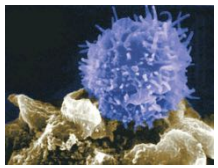
EXOGENOUS HUMANIZATION



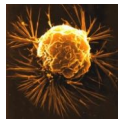
Human product

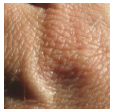
XENOGRAFT HUMANIZATION





Human hematopoietic cells (CD34⁺ HSPC; PBMC; ...)





Other tissues Tumors (PDX)

Immuno-deficient mouse strains

Timeline | **Important events in the development of humanized mice**

Shultz (2007), Nat. Rev. Immunol., 7:118

- 1966 — Description of the nude mutation[136]
- 1983 — Description of the CB17-*scid* mouse strain[1]
- 1988 — CB17-*scid* mice engrafted with human fetal tissues, adult blood cells and HSCs[2–4]
- 1992 — *Rag1*- and *Rag2*-targeted mutations described[7,8]
- 1995 — (1995–1999). *Il2rg*-targeted mutation made by four labs[19–22]; Description of NOD-*scid* mice and increased engraftment of human PBMCs and HSCs[9,10,12,13]
- 1997 — Description of NOD-*scid B2m*$^{-/-}$ mice[49]
- 2000 — Description of NOD-*Rag1*$^{-/-}$ mice[29]
- 2002 — (2002–2005). Description of the BALB/c-*Rag2*$^{-/-}$ *Il2rg*$^{-/-}$, NOD/Shi-*scid Il2rg*$^{-/-}$ and NOD/LtSz-*scid Il2rg*$^{-/-}$ mouse models and reports of a functional human immune system after human HSC engraftment[14–17,24]
- 2003 — Description of NOD–*Rag1*$^{-/-}$ *Prf1*$^{-/-}$ mice[48]
- Future — Pre-clinical bridge between mouse and human

SCID → NOD/SCID → NSG/NOG → BRG → BRGS(+)



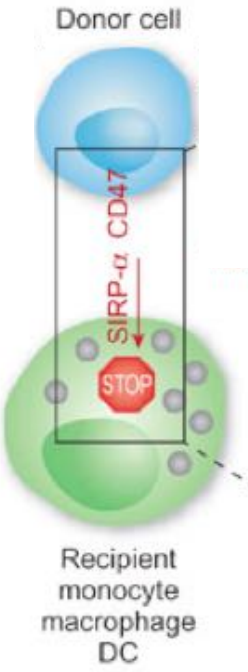


Hematopoietic reconstitution efficiency:
SCID < NOD/SCID < BRG < NSG/NOG, BRGS
(no mouse T/B/NK cells & tolerant phagocytes)

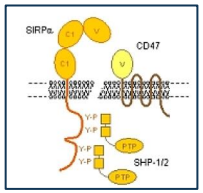
mouse T/B/NK

BRG = BALB/c Rag2^{tm1Fwa} Il2rg^{tm1Cgn}
BRGS = BALB/c Rag2^{tm1Fwa} Il2rg^{tm1Cgn} Sirpa^{NOD}
NSG = NOD.Cg-Prkdc^{scid} Il2rg^{tm1Wjl}/SzJ
NOG = NOD/Shi-scid Il2rg^{null}

The BRGS mouse strain

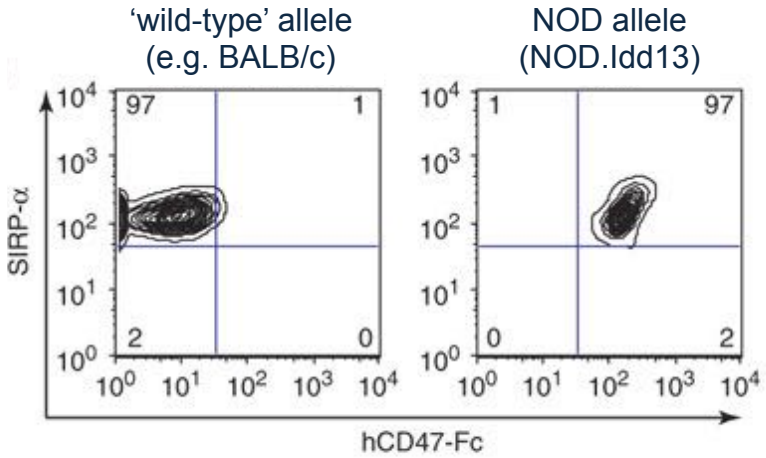


Effective CD47/SIRPα interaction to inhibit mouse phagocyte activity towards the human xenograft



'Do-not-eat-me'

Takizawa & Manz (2007), Nat. Immunol., 8:1287



Takenada (2007), Nat. Immunol., 8:1313

NOD
Rag2$^{-/-}$IL-2Rγc$^{-/-}$

(BRG)
BALB/c
Rag2$^{-/-}$IL-2Rγc$^{-/-}$

NODxBALB/c NOD.sirpa$^{+/-}$
Rag2$^{-/-}$IL-2Rγc$^{-/-}$ (N1)

BALB/c
Rag2$^{-/-}$IL-2Rγc$^{-/-}$

-> Speed congenic (BALB/c)
-> SIRPα^{NOD} allele screening (PCR)

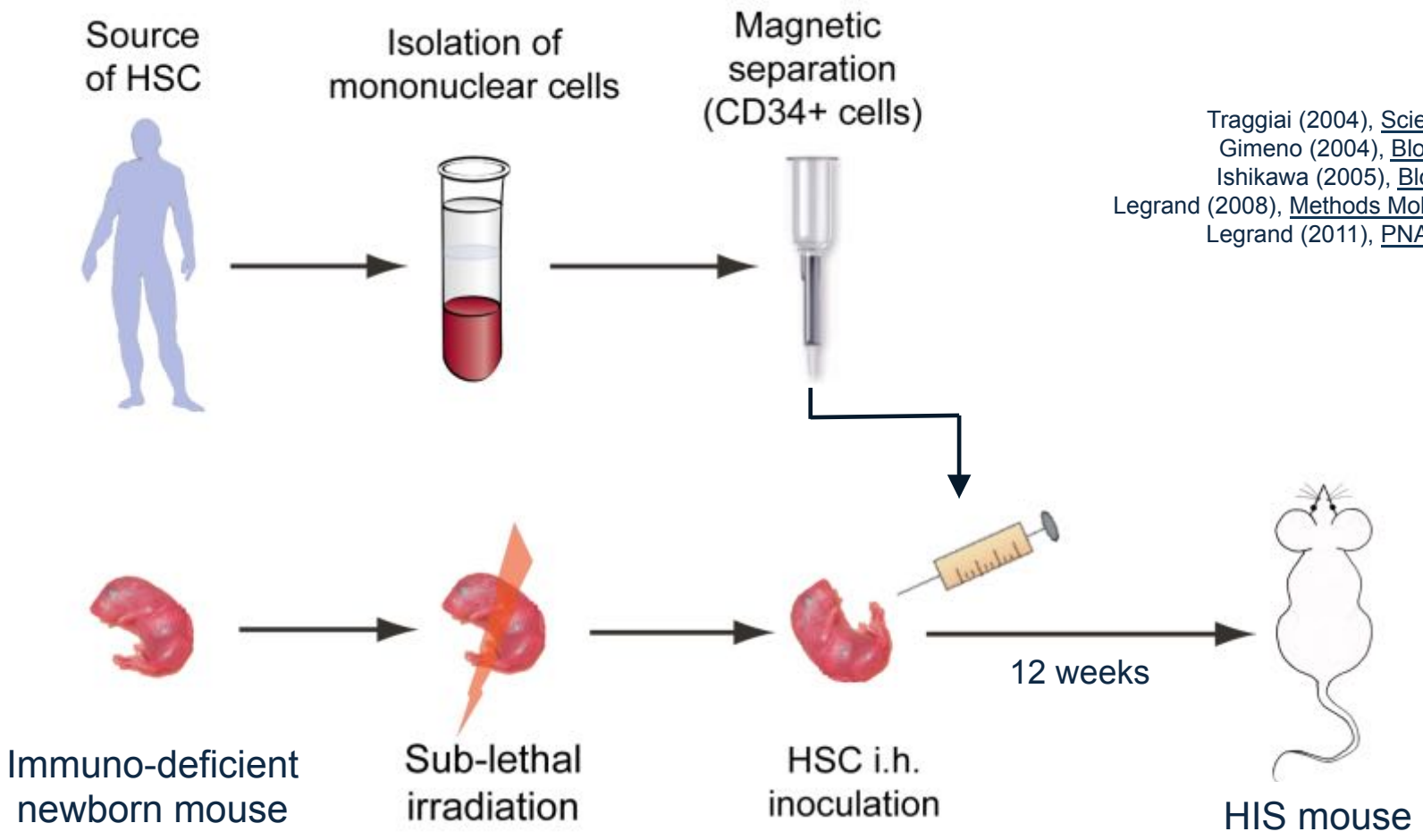
BRGS mice

[BALB/c Rag2^{tm1Fwa} Il2rg^{tm1Cgn} Sirpa^{NOD}]

- no mouse T/B/NK cells
- tolerant mouse phagocytes

Legrand (2011), PNAS, 108:13224

A simple strategy for HIS mouse generation

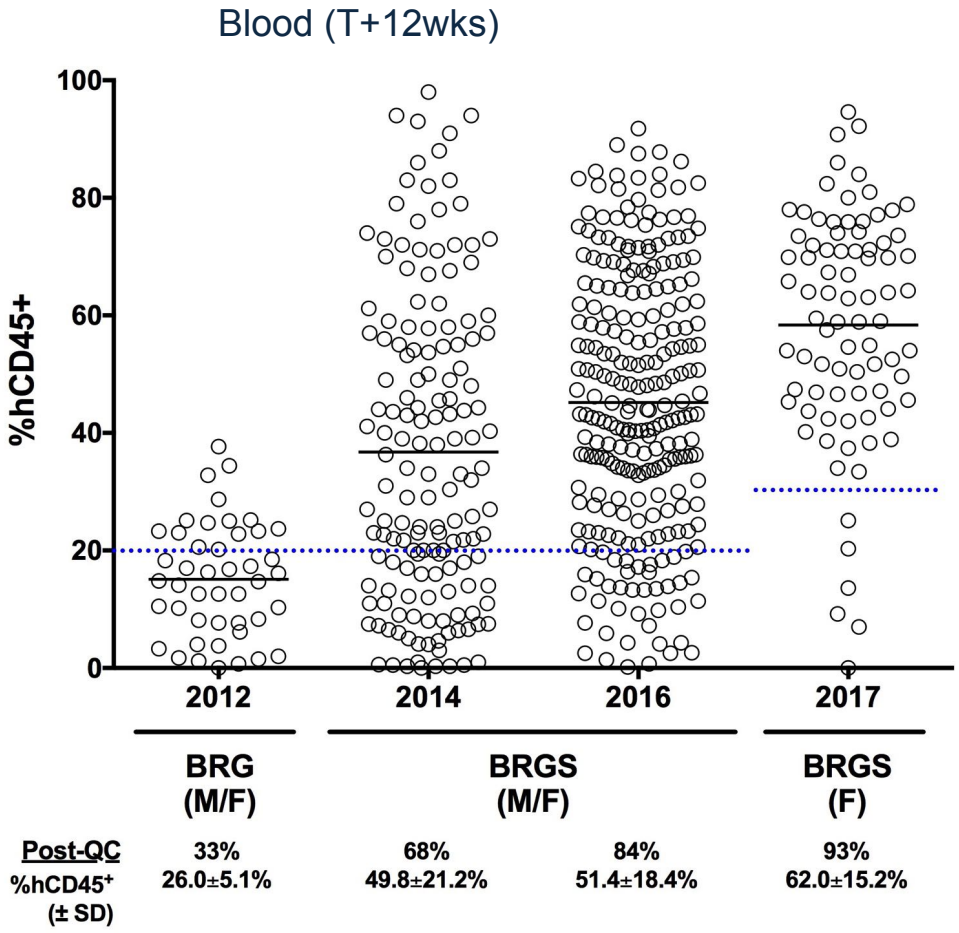


Traggiai (2004), Science, 304: 104
Gimeno (2004), Blood, 104: 3886
Ishikawa (2005), Blood, 106:1565
Legrand (2008), Methods Mol. Biol., 415:65
Legrand (2011), PNAS, 108:13224

Human hematopoietic reconstitution
(multi-lineage; multi-organ)

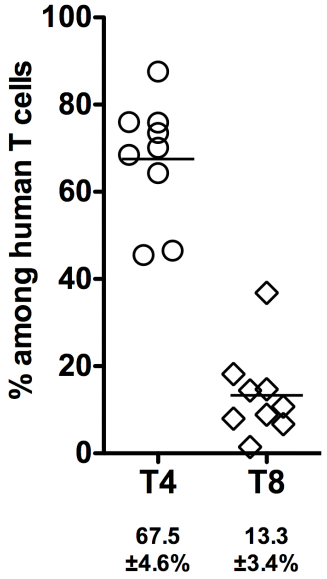
HSC = Hematopoietic Stem Cells
i.h. = intra-hepatic
HIS = Human Immune System

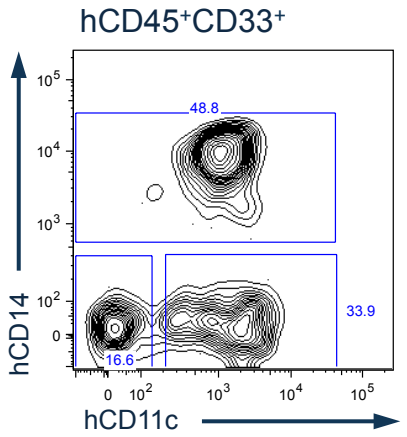
High human reconstitution level in BRGS-HIS mice



Subset distribution (blood, T+12wks)

- ✓ B cells 59.8 ± 7.7%
- ✓ T cells 10.7 ± 8.0%
- ✓ cDC 1.9 ± 0.6%





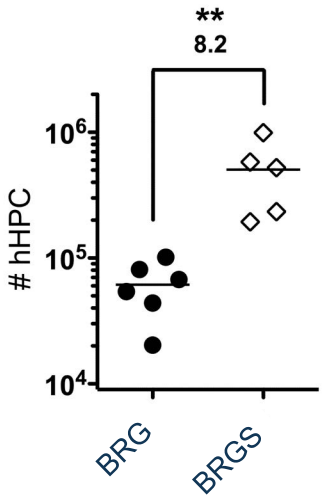
- ✓ HIS mice are routinely generated in females only;
- ✓ >95% of the HIS mice contain >30% hCD45+ leucocytes in blood at 12wks of age;

Restored human leucocyte homeostasis in BRGS mice

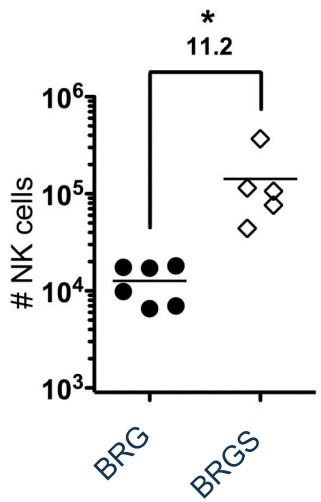
Total hCD45$^+$
(fold increase over control BRG-HIS mice)

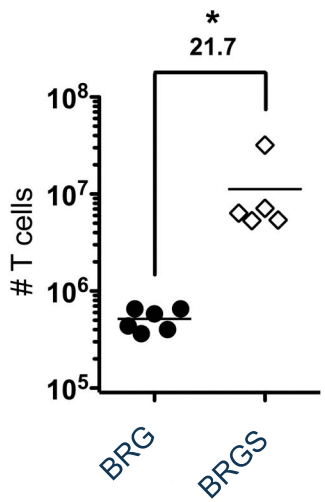
- ✓ BM: 2.5-fold
- ✓ Thymus: 2.0-fold
- ✓ Spleen: 7.5-fold
- ✓ Lymph nodes: 5-fold

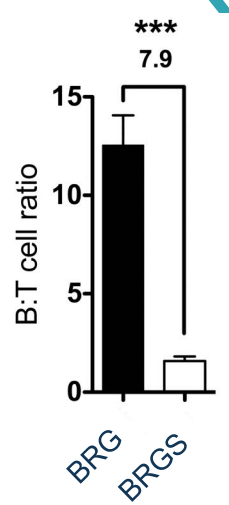
BM (T+12wks)



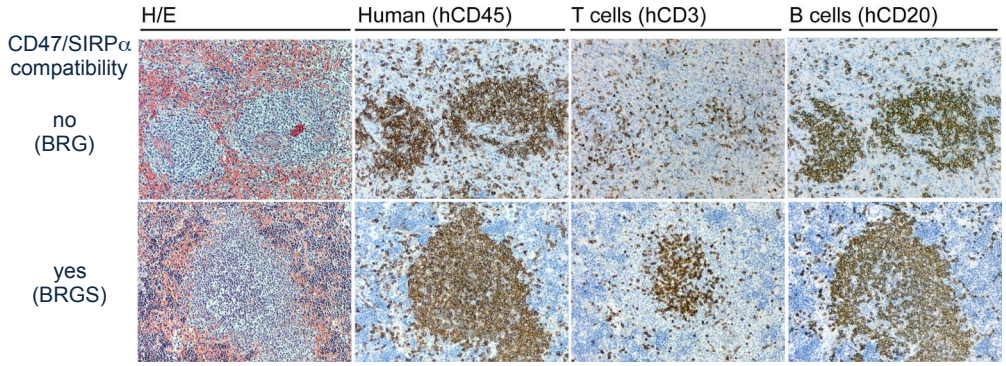
Spleen (T+12wks)

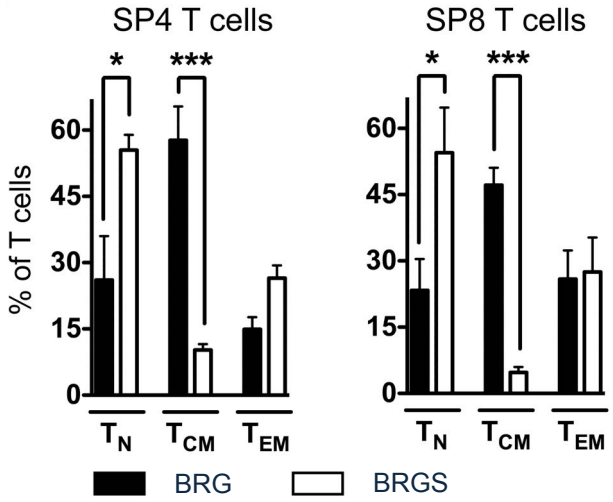






- ✓ Improved engraftment and accumulation of human hematopoietic progenitor cells (hHPC)
- ✓ Enhanced accumulation of all human hematopoietic subsets, in particular T & NK cells
- ✓ Selective improvement of T cell homeostasis

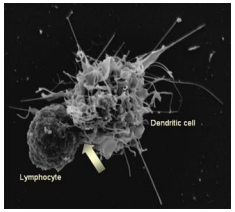




Legrand (2011), PNAS, 108:13224

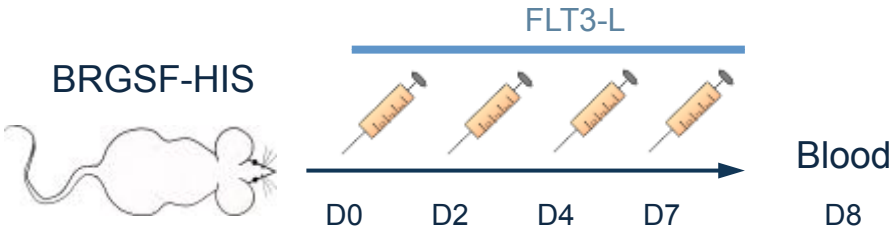
BRGSF-HIS mice for enhanced human DC density

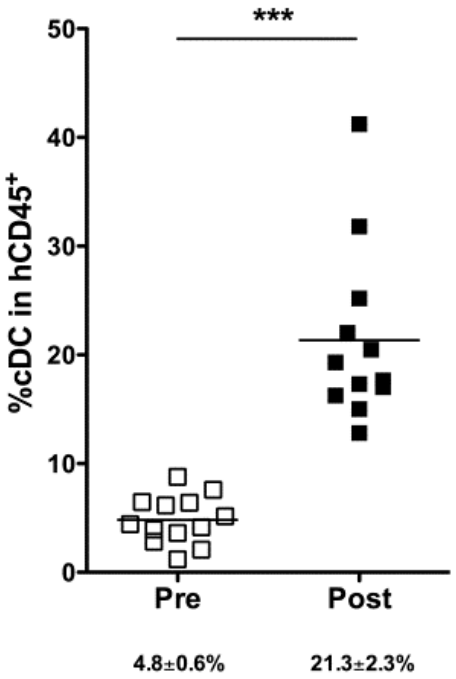
DC niche



Tilting the balance towards higher density of human DC in HIS mice

- ✓ the cytokine FLT3L/FLK2L is crucial for steady-state dendritic cell development;
- ✓ mouse and human FLT3L are highly homologous (cross-reactive);
- ✓ FLK2$^{-/-}$ mice show reduced numbers of mouse DC;
- ✓ “human DC boost on demand” hFLT3L injection into HIS mice increases human DC numbers



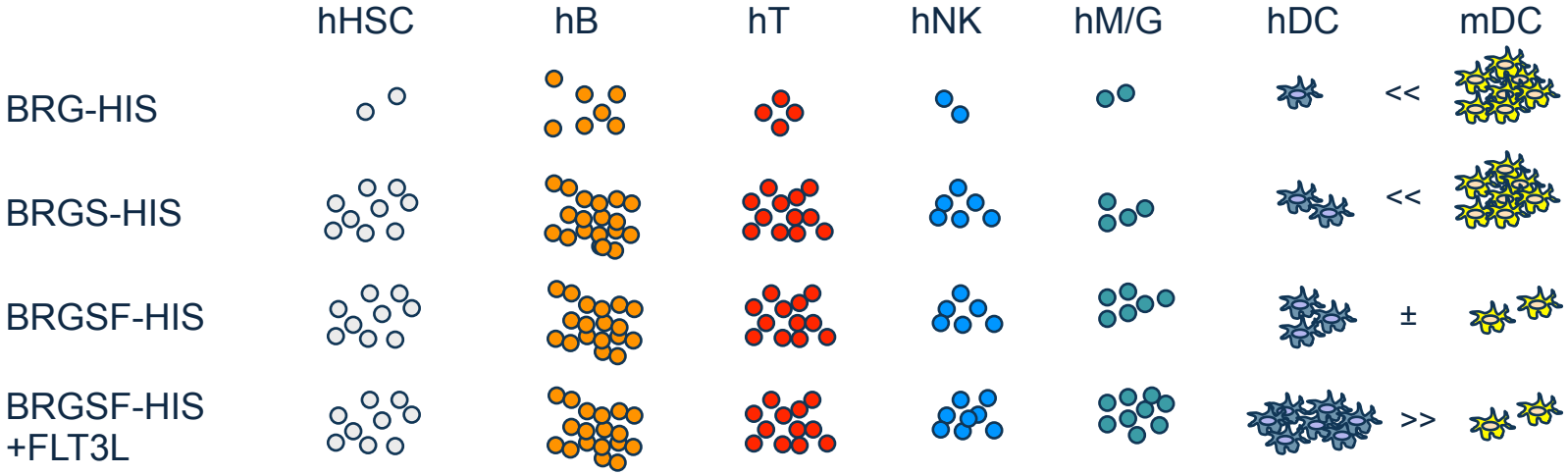


BRGSF mice

BRGSF = BALB/c Rag2^{tm1Fwa} Il2rg^{tm1Cgn} Sirpa^{NOD} Flk2^{tm1Irl}

Li (2016), EJI, 46:1291

Human leukocyte reconstitution – optimization strategies



Identification of limiting factors for human leukocyte homeostasis in BRG-HIS mice:

✓ Human cytokine bio-availability:

- IL-7 (thymopoiesis; αβ T cells)
- IL-15/IL-15Rα (thymopoiesis; memory αβ T4/T8; T γδ; NK)
- TPO (hHSC)
- IL-3/GM-CSF; M-CSF (myeloid cells)
- FLT3-L (cDC; pDC; mono/granulocytes; NK)

✓ Human dendritic cell density (αβ T cells)

✓ Human MHC expression (αβ T cells)

✓ Compatible CD47/SIRPα signaling axis (mouse phagocyte tolerance)

all human cell subsets benefit from this single modification

Legrand (2009), Cell Host & Microbe, 6:5
Huntington (2009) JEM, 206:25
van Lent (2009), J. Immunol., 183:7645
Chen (2009), PNAS, 106:21783
Strowig (2009), JEM, 206:1423
Shultz (2010), PNAS, 107:13022
O'Connell (2010), PLOS ONE, 5:e12009
Rongvaux (2011), PNAS, 108:2378
Willinger (2011), PNAS, 108:2390
Huntington (2011), PNAS, 108:6217
Legrand (2011), PNAS, 108:13224
Strowig (2011), PNAS, 108:13218
Huntington (2011), EJI, 41:2883
Suzuki (2012), Int. Immunol, 24:243
Li (2013), J. Immunol., 191:3192
Ding (2014), J. Immunol., 192:1982
Li (2016), Eur. J. Immunol., 46:1291

A flexible tool for research & industrial applications

‘Ready-to-use’ immuno-deficient mice
Delivery to end-users

Human Immune System mice

CRO services for outsourced R&D

Experimental human hematopoiesis
human hematopoietic cell maintenance, differentiation and function

Infectious diseases
Screening of new anti-viral compounds, microbicides, antibiotics; prospective experimentation for various human leucocyte-tropic pathogens
HIV, DNV, HTLV, EBV, HCMV, Yellow fever, Measles
S. Typhi, M. Tuberculosis,…

Pre-clinical POC
candidate vaccines; bio-therapeutics & mAbs; gene therapy; immunogenicity; adjuvants; immuno-modulatory molecules; inflammation;

Host-tumor interactions
Dual tumor/HIS models for the evaluation of new anti-tumor compounds relying on the activity of human immune cells (cell lines & personalized PDX);

‘Ready-to-use’ HIS mice
Delivery to end-users
(‘humanization factory’)

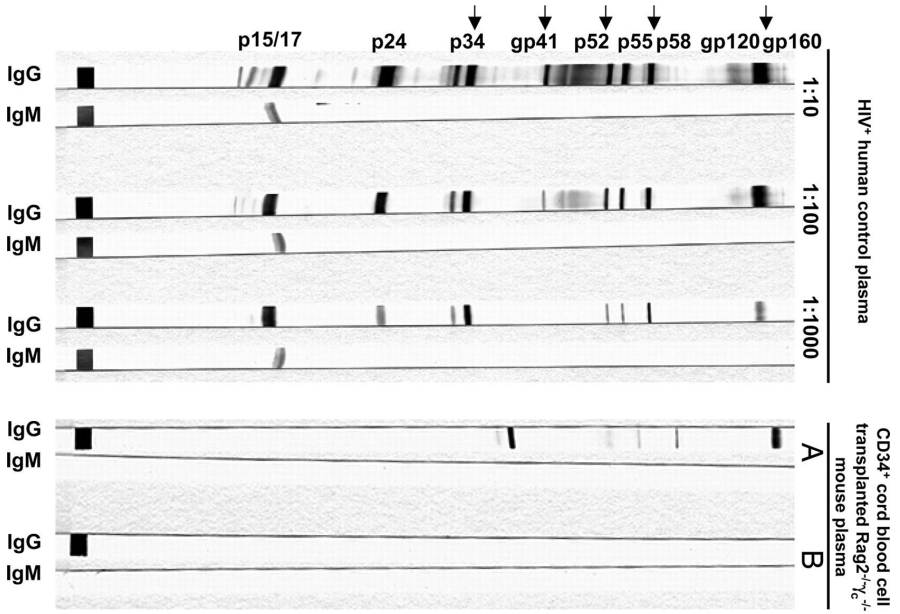
Human immune responses in HIS mice

- ✓ commercial TT vaccine, 1/10 of the human dose i.p. per injection (1 immunization + 2 boosts)
- ✓ analysis 10 days after last boost (5-6 wks after onset of vaccination)

	M1	M2	M3	M4	M5	human adults, n=5 mean (range)
age at start of vaccination (weeks)	12	17	17	15	12	-
human CD45$^+$ spleen cells (%)	85	12	38	25.5	77	-
human CD19$^+$ spleen cells (%)	37	2	9	13	38	-
human CD3$^+$ spleen cells (%)	46	8.5	22.3	8.1	6.5	-
Total IgG (µg/ml)	45	500	80	100	15	8600 (7500-10000)
TT specific IgG (µg/ml)	0.1	ND	ND	0.3	0.2	33 (16-75)
TT specific IgG/total IgG	1:450	-	-	1:333	1:75	1:260

Traggiai (2004), Science, 304:104

- ✓ poor anti-HIV B cell response (IgG in 1/25 YU-2/R5 infected animals)

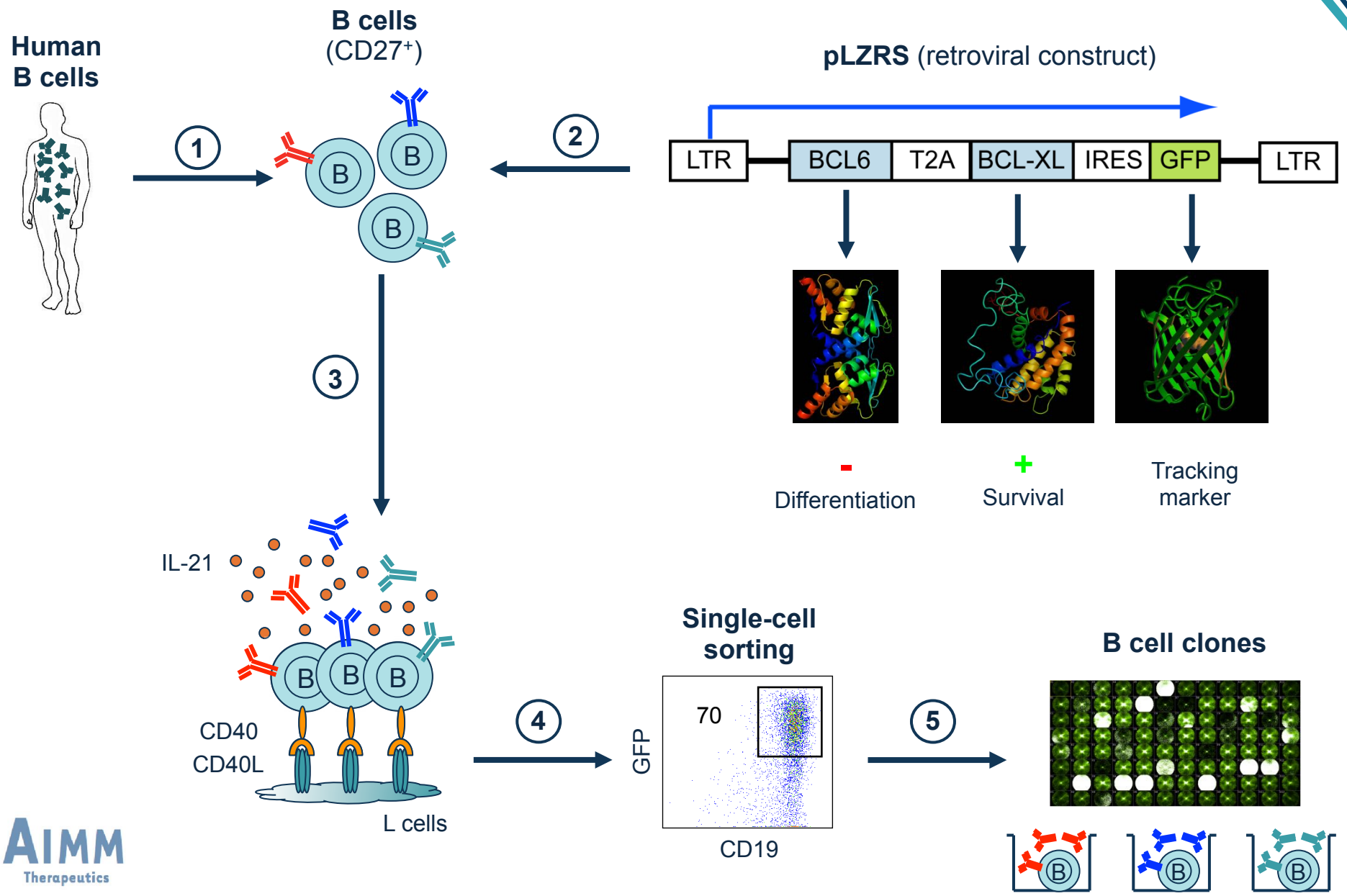


Baenziger (2006), PNAS, 103: 15951

- ✓ weak responses ~0.2-1% specific IgG levels of vaccinated humans
- ✓ low efficiency of i.p. route 5-10% responder HIS mice
- ✓ no/weak anti-HIV T cell response
- ✓ similar results with other model pathogens e.g. measles; influenza; yellow fever

Analysis of B cell responses at clonal level

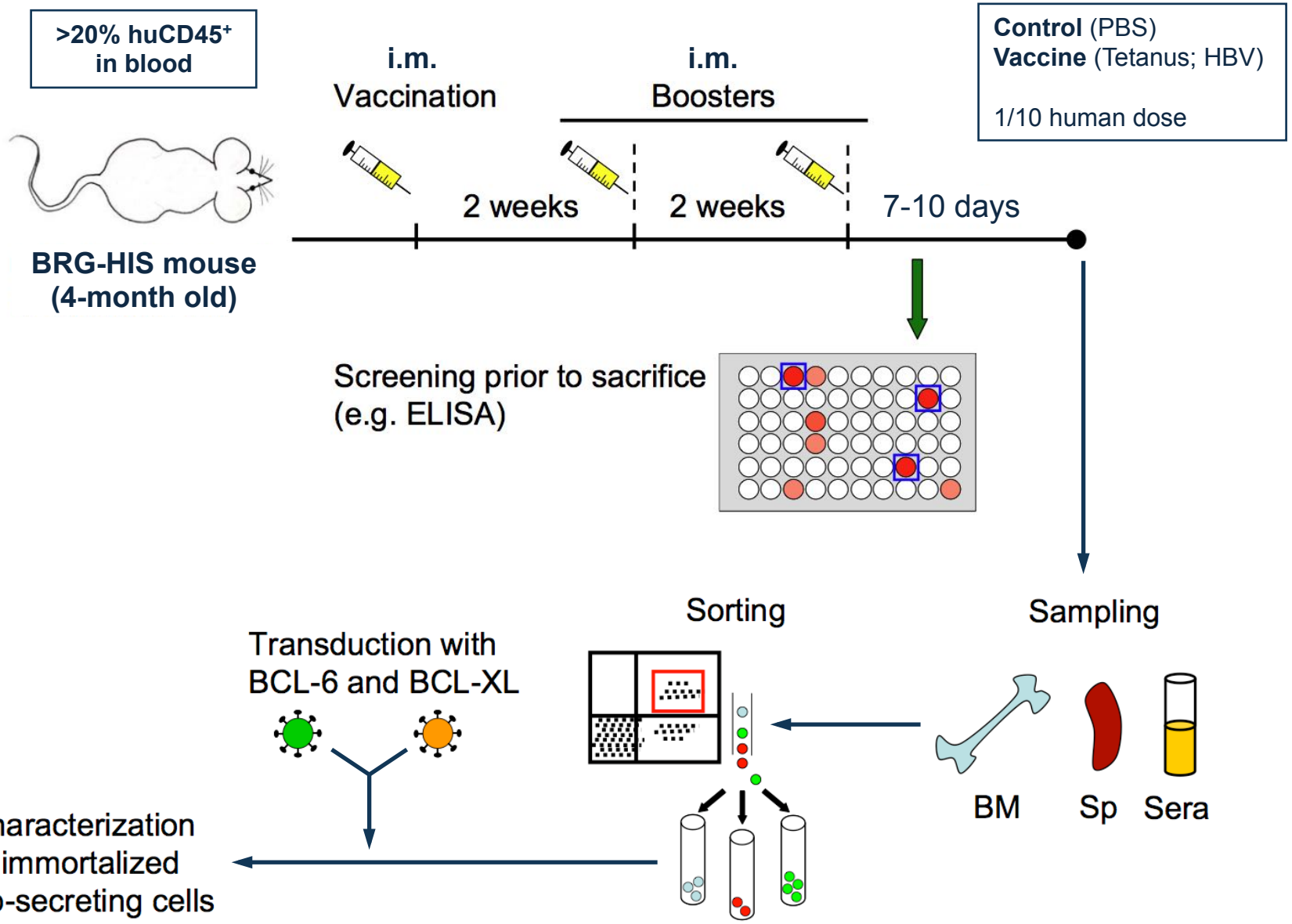
From primary B cells to human monoclonal antibodies



AIMM Therapeutics

Kwakkenbos & Diehl (2009), Nat.Med., 16:123

Vaccination scheme

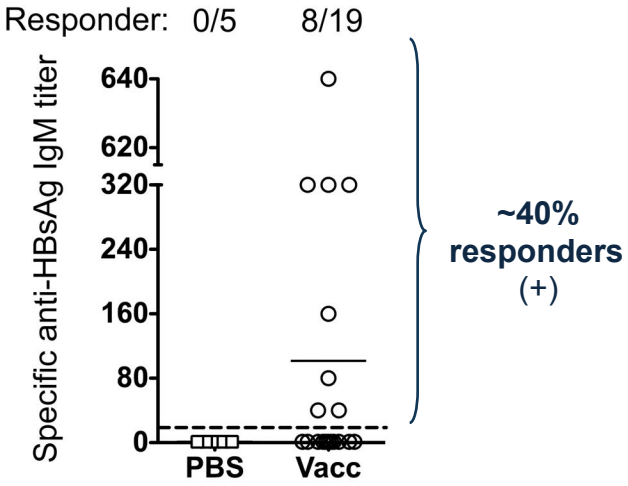


Becker & Legrand (2010), PLoS ONE, 5:e13137

Immunological parameters after vaccination

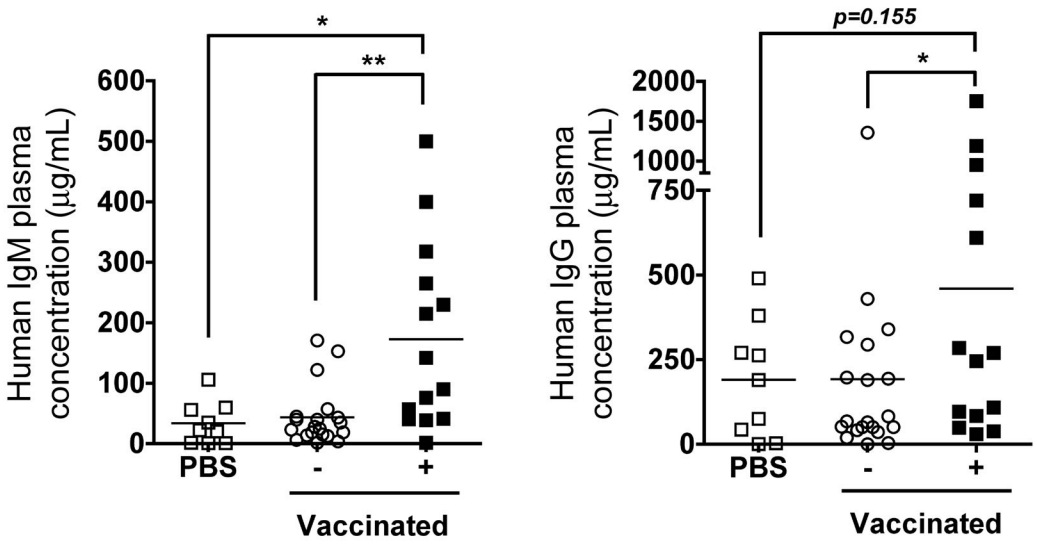
Plasma (Ag-specific Ig)

HBsAg IgM ELISA



Plasma (total Ig)

HIS (BALB-Rag/γ) after vaccination

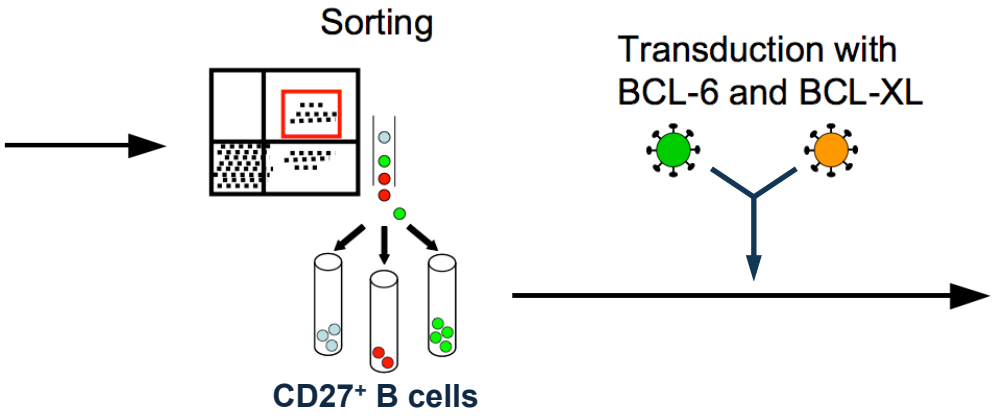


Spleen

Groups	Human cells (CD45⁺)		
	Total	B cells (CD19⁺)	T cells (CD3⁺)
	Absolute number (×10⁶)	Absolute number (×10⁶)	Absolute number (×10⁶)
Controls (n = 10)	0.72±0.27	0.25±0.16	0.43±0.15
Vaccinated (n = 34)	3.63±0.75 **	2.03±0.46**	1.45±0.41 *n.s.*
Responders (n = 14)	5.63±1.54 **	3.06±0.96**	2.44±0.87 *
non-responders (n = 20)	2.06±0.45*	1.28±0.35**	0.59±0.20 *n.s.*

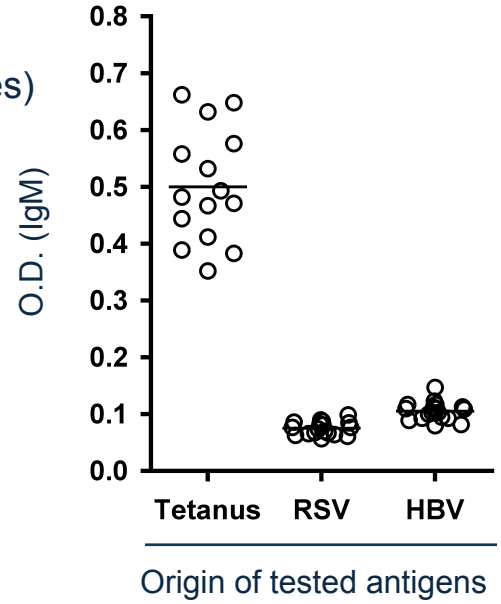
Becker & Legrand (2010), PLoS ONE, 5:e13137

Antigen-specific B cell clones generated from HIS mice

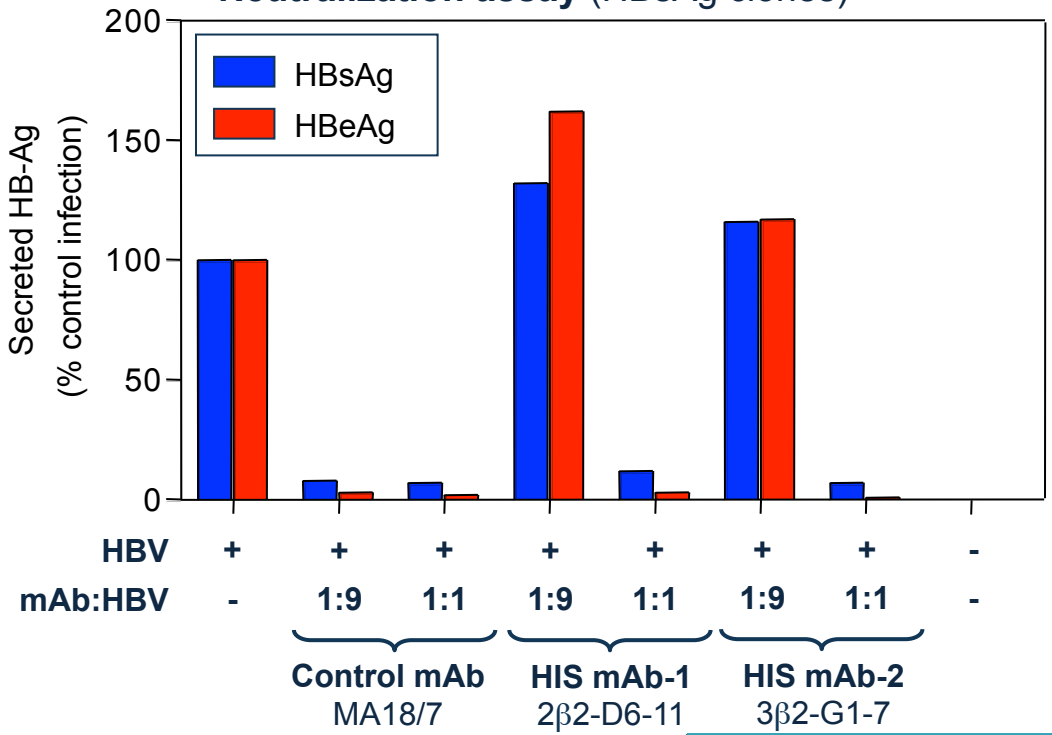


B cell clones:
15 HBsAg-specific, IgM+
18 TT-specific, IgM+
(frequency ~1:250)

ELISA
(TT clones)



Neutralization assay (HBsAg clones)



Becker & Legrand (2010), PLoS ONE, 5:e13137

All clones show low levels of hypersomatic mutations

IgM V_H amino-acid sequence
(HBsAg-specific B cell clones)

CLONES	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
VH3-73	**EVQLVESGGGLVQPGGSLKLSCAAS**	**GFTFSGSA**	**MHWVRQASGKGLEWVGR**	**IRSKANSYAT**	**AYAASVK GRFTISRDDSKNTAYLQMNSLKTEDTAVYYC**	**TR**	**WGQGTLVTVSS**
6β2-D4-3	GGGLVQPGGSLKLSCAAS	GFTFSGSA	MHWVRQASGKGLEWVGR	IRSKANSYAT	AYAASVK GRFTISRDDSKNTAYLQMNSLKTEDTAVYYC	TSRKSSSSDY	WGQGTLVTVSS
6β1-E3-10	EVQLVESGGGLVQPGGSLKLSCAAS	GFTFSGSA	MHWVRQASGKGLEWIGR	IGSKANSYAT	AYAAPVK GRFTISRDDSKNTAYLQMNSLKTEDTAVYYC	TSRKSSSSDY	WGQGTLVTVSS
3β2-F2-2	EVQLVESGGGLVQPGGSLKLSCAAS	GFTFSGSA	MHWVRQASGKGLEWVGR	IRSKPNSYAT	AYAASVK GRFTISRDDSKNTAYLQMNSLKTEDTAVYYC	TRLSGRGVDY	WGQGTLVTVSS
6β2-G11-6	EVQLVESGGGLVQPGGSLKLSCAAS	GFTFSGSA	MHWVRQASGKGLEWVGR	IRSKANSYAT	AYAASVK GRFTISRDDSKNTAYLQMNSLKTEDTAVYYC	TRKSSSSDY	WGQGTLVTVSS
5β2-D5-5	EVQLVESGGGLVQPGGSLKLSCAAS	GFTFSGSA	MHWVRQASGKGLEWVGR	IRSKANSYAT	AYAASVK GRFTISRDDSKNTAYLQMNSLKTEDTAVYYC	TRTYSSSWYFDY	WGQGTLVTVSS
γ5-8	EVQLVESGGGLVQPGGSLKLSCAAS	GFTFSGSA	MHWVRQASGKGLEWVGR	IRSKANSYAT	AYAASVK GRFTISRDDSKNTAYLQMNSLKTEDTAVYYC	TRTYSSSWYFDY	WGQGTLVTVSS
γ6-7	EVQLVESGGGLVQPGGSLKLSCAAS	GFTFSGSA	MHWVRQASGKGLEWVGR	IRSKANSYAT	AYAASVK GRFTISRDDSKNTAYLQMNSLKTEDTAVYYC	TRRGYYGSGSYYGDY	WGQGTLVTVSS
5β1-E3-5	EVQLVESGGGLVQPGGSLKLSCAAS	GFTFSGSA	MHWVRQASGKGLEWVGR	IRSKANSYAT	AYAASVK GRFTISRDDSKNTAYLQMNSLKTEDTAVYYC	TRRGYYGSGSYYGDY	WGQGTLVTVSS
VH4-34	**QVQLQQWGAGLLKPSETLSLTCAVY**	**GGSFSGYY**	**WSWIRQPPGKGLEWIGE**	**INHSGST**	**NYNPSLK SRVTISVDTSKNQFSLKLSSVTAADTAVYYC**	**AR**	**WGQGTLVTVSS**
2β2-D6-11	QVQLQQWGAGLLKPSETLSLTCAVY	GGSFSVYY	WSWIRQPPGKGLEWIGK	INHSGST	NYNPSLK SRVTISVDTSKNQFSLKLSSVTAADTAVYYC	ARGFHY	WGQGTLVTVSS
VH3-30	**QVQLVESGGGVVQPGRSLRLSCAAS**	**GFTFSSYG**	**MHWVRQAPGKGLEWVAV**	**ISYDGSNK**	**YYADSVK GRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**	**AR**	**WGQGTLVTVSS**
3β2-G1-7	QVQLVESGGGVVQPGRSLRLSCAAS	GFTFSSYG	MHWVRQAPGKGLEWVAV	ISYDGSNK	YYADSVK GRFTISRDNSKNTLYLQMNSLRAEDTAVYYC	AKAVVDRARDGYNLGY	WGQGTLVTVSS
γ6-14	PGRSLRLSCAAS	GFTFSTYA	MHWVRQAPGKGLEWVAV	ISYDGSNK	YYADSVK GRFTISRDNSKNTLYLQMNSLRAEDTAVYYC	ARGTYYGSGIGFDY	WGQGTLVTVSS
VH3-15	**EVQLVESGGGLVKPGGSLRLSCAAS**	**GFTFSNAW**	**MSWVRQAPGKGLEWVGR**	**IKSKTDGGTT**	**DYAAPVK GRFTISRDDSKNTLYLQMNSLKTEDTAVYYC**	**TT**	**WGQGTLVTVSS**
2β2-H8-2	EVQLVESGGGLVKPGGSLRLSCAAS	GFTFSNAW	MSWVRQAPGKGLEWVGR	IKSKTDGGTT	DYAAPVK GRFTISRDDSKNTLYLQMNSLKTEDTAVYYC	LINWGIRD	WGQGTLVTVSS
γ2-15	GSLRLSCAAS	GFTFSNAW	MSWVRQAPGKGLEWVGR	IKSKTDGGTT	DYAAPVK GRFTISRDDSKNTLYLQMNSLKTEDTAVYYC	LINWGIRD	WGQGTLVTVSS
VH5-51	**EVQLVQSGAEVKKPGESLKISCKGS**	**GYSFTSYW**	**IGWVRQMPGKGLEWMGI**	**IYPGDSDT**	**RYSPSFQ GQVTISADKSISTAYLQWSSLKASDTAMYYC**	**AR**	**WGQGTLVTVSS**
γ1-4	EVQLVQSGAEVKKPGESLKISCKGS	GYSFTTYW	IGWVRQMPGKGLEWMGI	IYPGDSDT	RYSPSFQ GQVTISADKSISTAYLQWSSLKASDTAMYYC	ARHSEYYYDSSGYYLDY	WGQGTLVTVSS
VH5-A	**EVQLVQSGAEVKKPGESLRISCKGS**	**GYSFTSYW**	**ISWVRQMPGKGLEWMGR**	**IDPSDSYT**	**NYSPSFQ GHVTISADKSISTAYLQWSSLKASDTAMYYC**	**AR**	**WGQGTLVTVSS**
γ6-21	EVQLVQSGAEVKKPGESLRISCKSS	GYSFTSYW	ISWVRQMPGKGLEWMGR	IDPSDSYT	KYSPSFQ GHVIISADKSISTAYLQWSSLKASDTAMYYC	ARHLREAVADFPMDV	WG

Becker & Legrand (2010), PLoS ONE, 5:e13137

Human immune responses in HIS mice

Human B cell responses are induced in HIS mice upon vaccination

✓ Human B cell responses are induced by various vaccines (OVA; KLH; TT; HBV; Flu)

✓ Immunization per i.m. route is more efficient than i.p. route

✓ Human antigen-specific B cells can be isolated and cloned from vaccinated HIS mice

✓ Optimized HIS mouse models with improved human cell homeostasis & function permit isolation of large numbers of antigen-specific B cell clones (including IgG^+)
e.g. in humanized BRGS mice

✓ The generated mAbs exhibit features of low affinity, close-to-germline antibodies
(limited germinal center reaction; limited Ig switch; limited affinity maturation process)

Optimizating immunization strategies

✓ Vaccination design
(protocols, timing, formulation, adjuvants)

✓ Incremental, step-wise optimization of new recipient mouse strains for improved xenograft features
(human cell content and function)

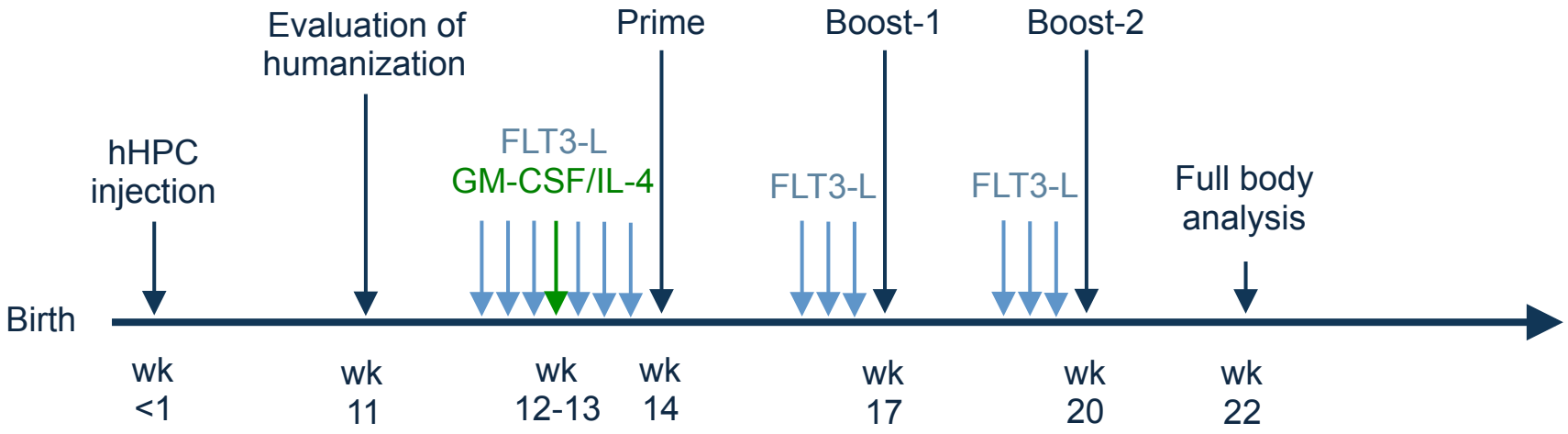
✓ Use of exogenous agonists of immune cells during immunization

Vaccination in hDC-boosted BRGSF-HIS mice

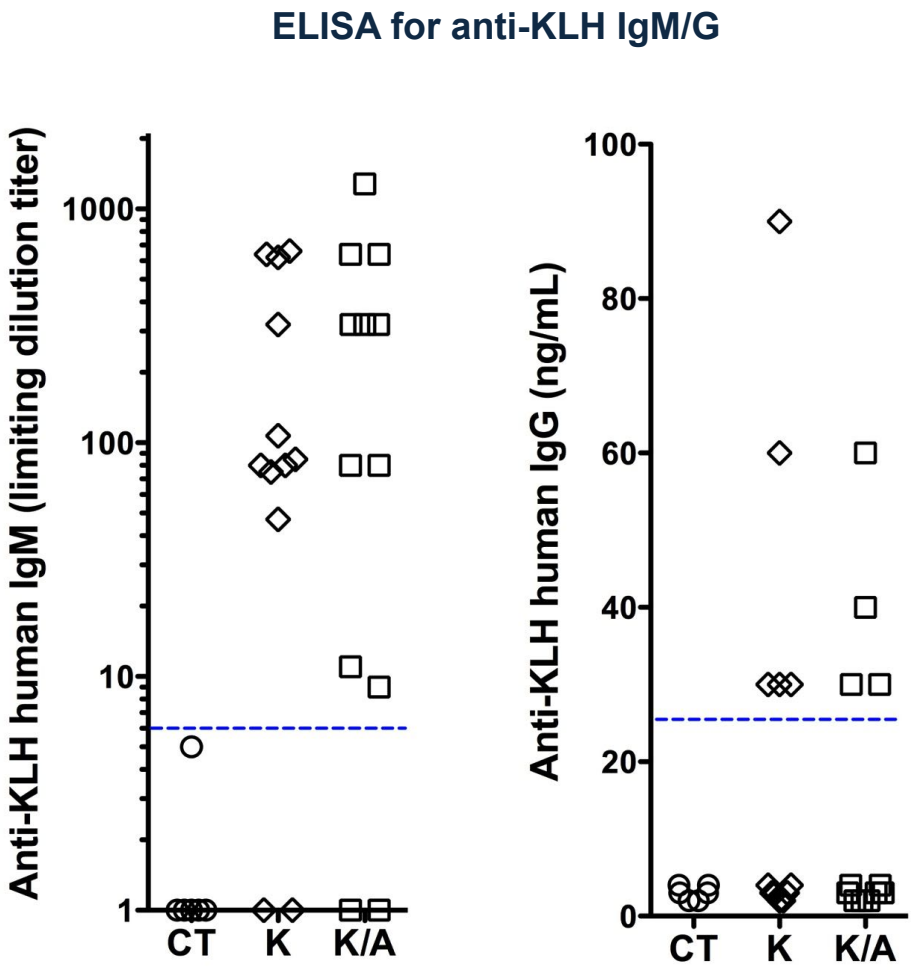
- ✓ Human antigen-presenting cells might represent a functional bottleneck – human DC boosting strategy?
- ✓ Model antigen: Keyhole Limpet Hemocyanin (~3400 a.a.; ~390kDa)
  KLH (K) vs. KLH/Alum (K/A)
- ✓ Exogenous agonists of immune cells before immunizations:
  soluble FLT3-L/Fc
  + hydrodynamic delivery of hGM-CSF/hIL-4 encoding DNA plasmids
- ✓ Standardized vaccination design

FLT3-L	more hDC
GM-CSF/IL-4	more mature hDC

Di Santo & Mention (2010), patent
Chen (2012), J. Immunol., 189:5223
Ding (2014), J. Immunol., 192:1982
Li (2016), Eur. J. Immunol. 46:1291



Human B cell responses to KLH



- ✓ Human IgM responses
  83% (20/24) responding animals in KLH-specific IgM ELISA
  vs. 20-40% w/o immuno-stimulation
- ✓ Human IgG responses
  45% (9/20) of the IgM-responder animals also exhibit anti-KLH IgG responses
  vs. almost no detectable IgG w/o immuno-stimulation
- ✓ Impact of adjuvant
  No benefit from alum

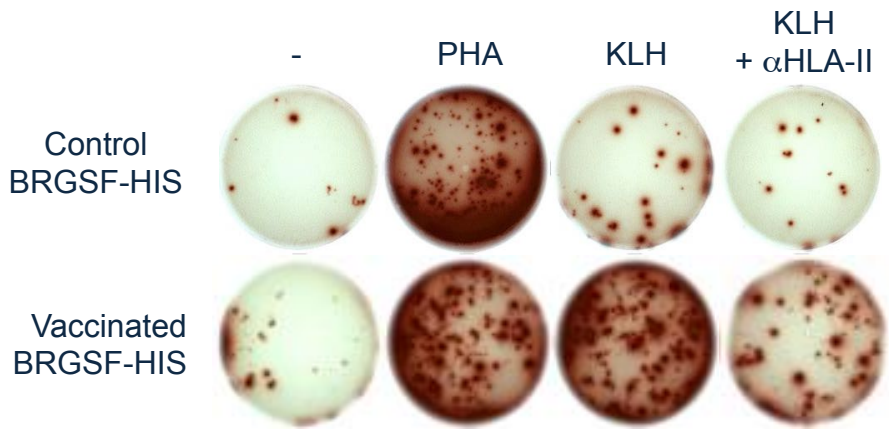
CT: PBS-injected
K: KLH-injected
K/A: KLH/alum-injected

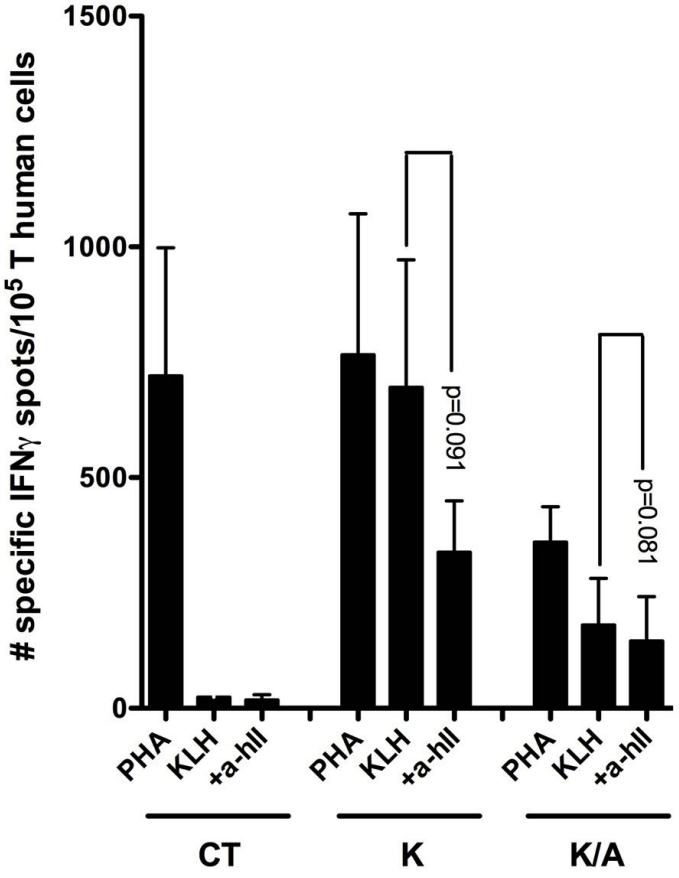
Human T cell responses to KLH

- ✓ Human T cell responses
  67% (14/21) of the animals show a T cell response to KLH
  vs. no detectable T cell responses without immuno-stimulation

- ✓ MHC restriction of T cell responses
  57% (8/14) of the responder animals show partial HLA class-II restriction (human DC biased?)
  HLA-class-I and mouse MHC restricted responses possible as well

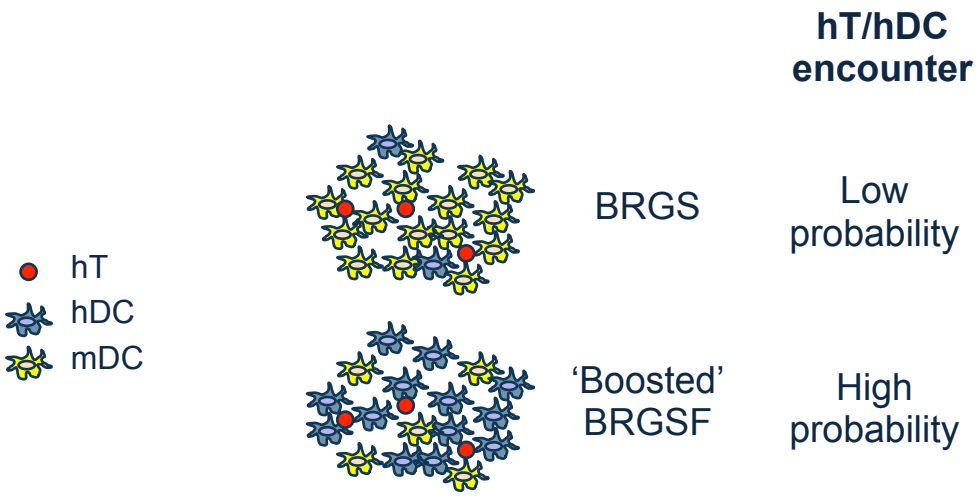
ELISPOT IFNγ
(spleen)





An unprecedented level of human immune responses

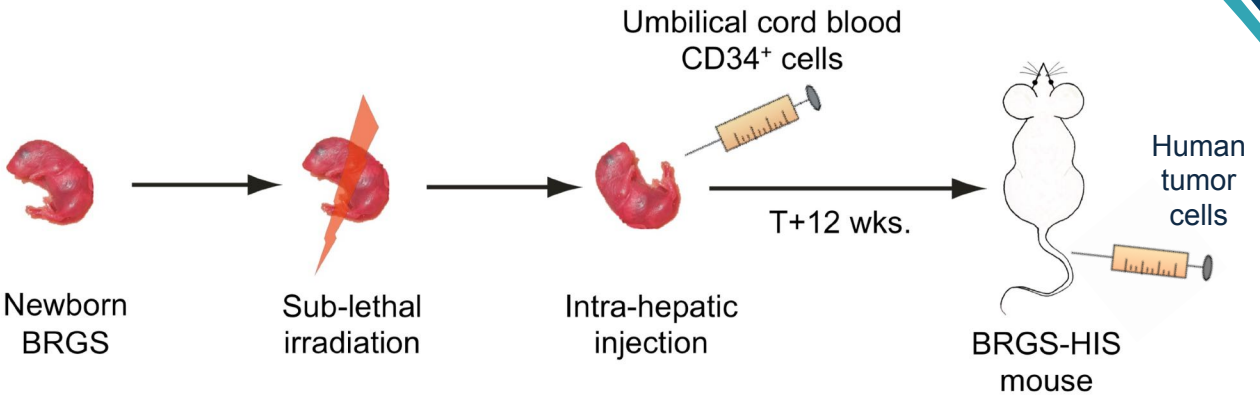
Enhancement of human dendritic cell density and maturation status has major functional benefits on human immune responses in HIS mice



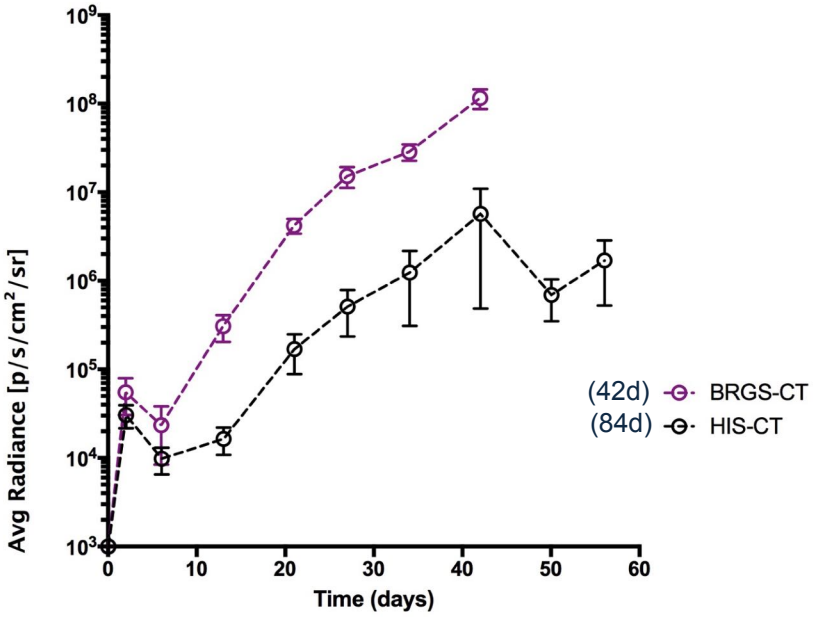
- ✓ Screening of candidate vaccines
- ✓ Validation of immuno-modulatory compounds
- ✓ Evaluation of new adjuvants
- ✓ Evaluation of compound immunogenicity
- ✓ Model limitations should be kept in mind…

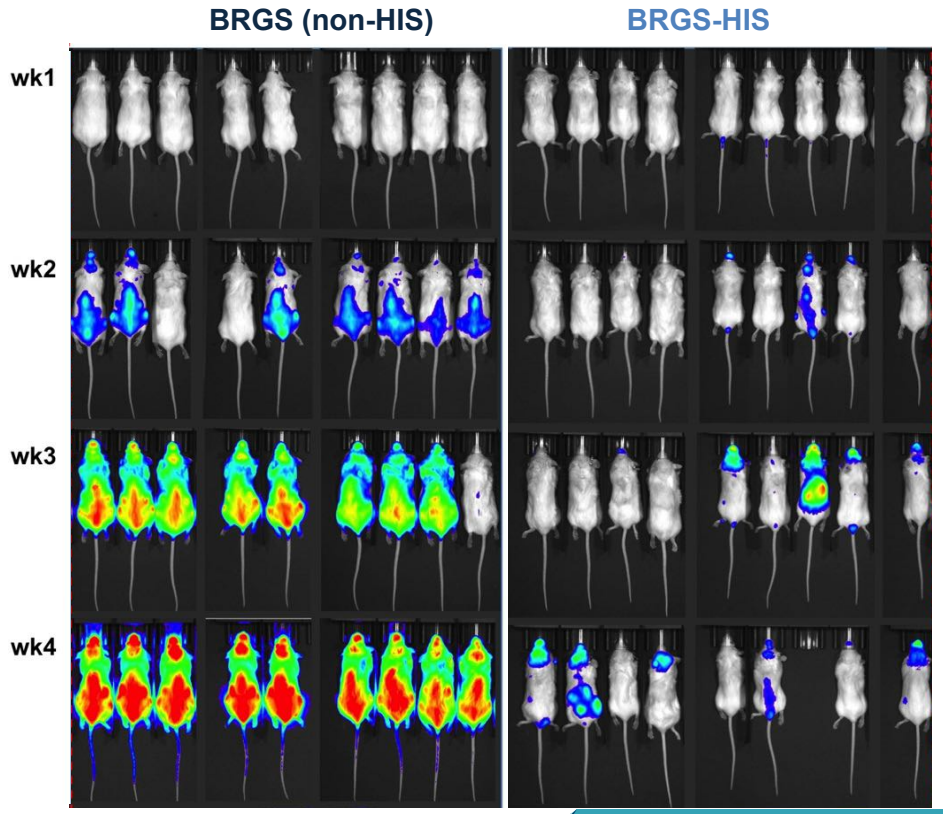
Human immune responses to tumor cells in HIS mice

- ✓ **'Double-humanized' mice**
  - Human immune system
  - Human tumor xenograft
- ✓ **Daudi-luc⁺ cell model**
  B cell leukemia (BCL) [i.v.]



- ✓ Tumor cell outgrowth
  Tumor cells can be tracked by bioluminescence
- ✓ Human immune cells limit tumor outgrowth





BCL/HIS mice for bispecific antibody POC study

✓ **Evaluation of treatment anti-tumor efficacy**
14-weeks old BRGS-HIS mice
5x10^6 Daudi-Luc$^+$ cells i.v.

Comparison of 3 Bs-mAbs
2 injections (d3/7; 1mg/kg i.v.)

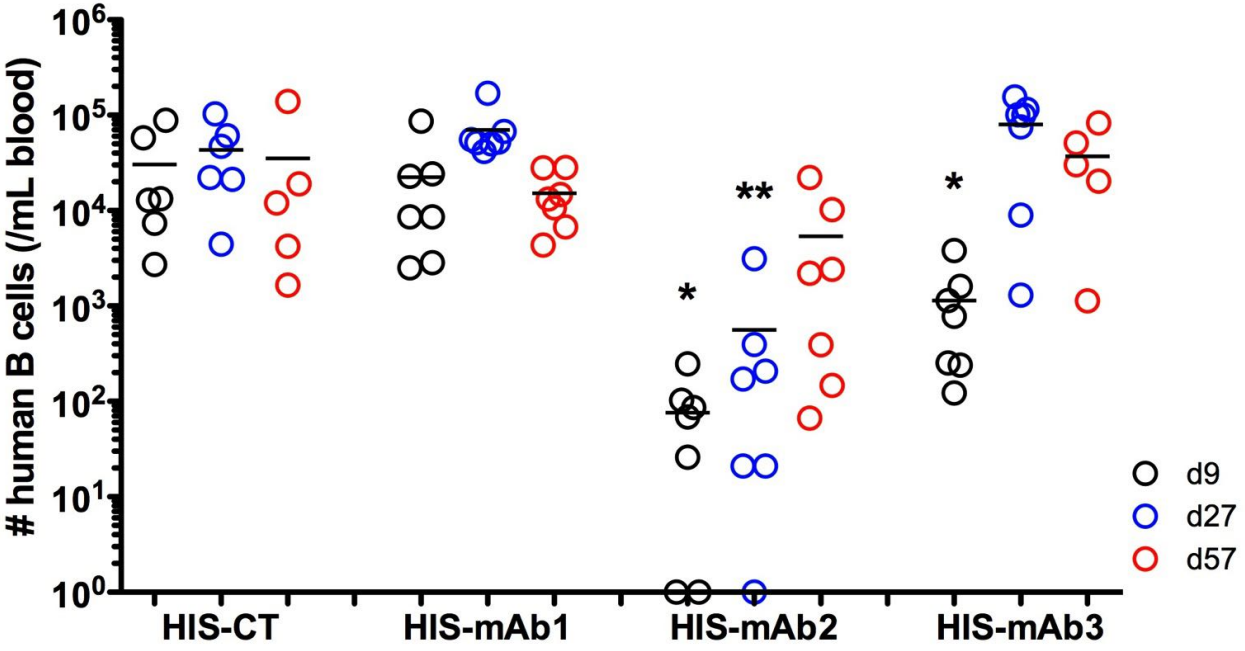
CT: PBS vehicle control

mAb1: human T cell targeting only (monovalent)

mAb2: human T cell + human B cell targeting (bispecific)

mAb3: human B cell targeting only (monovalent)

Human B cell depletion in blood
* p<0.05; ** p<0.01 (compared to HIS-CT)



✓ Transient B cell depletion activity is observed with the 2 B cell-targeting test products
(mAb2 & mAb3)

Genmab

BCL/HIS mice for bispecific antibody POC study

- ✓ **Evaluation of treatment anti-tumor efficacy**
  14-weeks old BRGS-HIS mice
  $5x10^6$ Daudi-Luc$^+$ cells i.v.

  Comparison of 3 Bs-mAbs
  2 injections (d3/7; 1mg/kg i.v.)

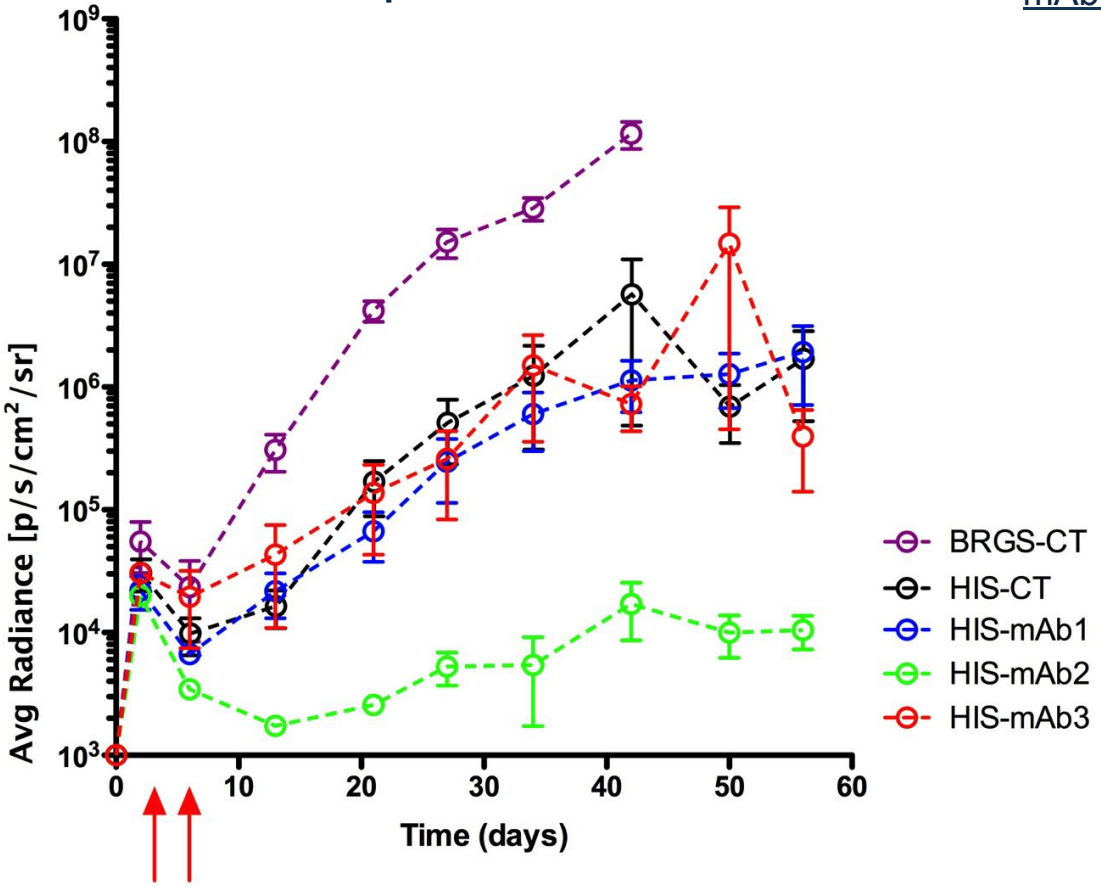
CT: PBS vehicle control

mAb1: human T cell targeting only (monovalent)

mAb2: human T cell + human B cell targeting (bispecific)

mAb3: human B cell targeting only (monovalent)

Tumor cell expansion



- ✓ Monovalent B cell targeting does not efficiently control tumor outgrowth (mAb3)
- ✓ Tumor control is only achieved when human T cells are recruited to the tumor B-cells by the bispecific antibody (mAb2)

Genmab

Conclusions

Human immune responses in HIS mice

✓ Human dendritic cells (number & maturation status) represent a limitation for the consistent generation of human antigen-specific immune responses in HIS mice

✓ Human B cell responses are induced upon vaccination, but remain weak/rare without immuno-stimulation

✓ Human antigen-specific B cells can be isolated and cloned from vaccinated HIS mice, but the generated mAbs exhibit features of low affinity, close-to-germline antibodies

✓ Human T cell responses are observed in a large majority of human DC-boosted animals

✓ A major field bottleneck has been removed with such an immuno-stimulatory approach

✓ Human immune cells efficiently respond to tumors (allogeneic tissues) and efficiently respond to anti-tumor, mAb-induced effector cell mobilization

Major model improvements over the past 30 years… and still ongoing

✓ Standardized HIS mouse production

✓ Optimized immuno-deficient mouse models with combined genetic/cellular humanization strategies

✓ Addressing the specific requirements/limitations of each application field

e.g. for immunogenicity assessment: expected frequency of response vs. batch size? Immune tolerance for tested products? Genetic variability of human HSC donors? Optimization of vaccination strategies?

“Human Immune System” mouse models for preclinical risk assessment

Nicolas LEGRAND, Ph.D. Director – Immunology

European Immunogenicity Platform
27-Feb-2019