From syngeneic to humanized mouse models: addressing the need for novel immunotherapies.

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17th WPC
June 18-21, 2018
BOSTON, MA

1. Oncodesign corporate introduction
2. Syngeneic tumor models
3. PDX model
4. Humanized mouse models

1 Oncodesign corporate introduction

ONCODESIGN: a sustainable industrial biotech focused on the discovery of new therapies

A track record and research operations in biotech clusters of excellence with a global reputation

1995
Creation of the company

€11.4 million
S1 2017 revenue

Positive net income
for the second successive year

215
Employees, with >20% PhDs

€4.7 million
Revenue invested in R&D in S1 2017

> 600
clients including 15 big pharma groups

5
Scientific and commercial partnerships

Bristol-Myers Squibb, ucb, CYCLOPHARMA, IMODI, OncoSNIPE

5
In-house *Drug Discovery* projects

PARIS SACLAY

Present at the heart of the Paris-Saclay bio-cluster

- 47 Oncodesign research scientists
- Based in Centre François Hyafil, a research center covering 11,000 m² that includes 7000 m² of ultramodern GSK laboratories
- Oncodesign teams integrated in Ipsen's *Open Innovation* campus

A commercial and production presence in the largest global market

- 7 research scientists in Synergie
- Production subsidiary in Montreal
- Commercial subsidiary in Boston, at the heart of the US biotech community

Dijon: historic roots in the University Hospital cluster

- 61 Oncodesign research scientists
- 3000 m2 of premises, opened in 2004

Oncodesign innovative technology platforms

- All integrated in a translational drug discovery engine

Chi-Mice
Humanised animal models
(PDX, immune system, organs)

OncoSnipe
Bio-informatics module to identify characteristics shared by sub-groups of patients who are resistant to available therapies

Nanocyclix
Medicinal chemistry: 7500+ macrocyclic kinase inhibitors

Pharmimage
Pharmaco-imaging modalities (preclinical and clinical) – including radiochemistry

Predict
Orientation platform: in vitro and in vivo pharmacology models (mouse and rat models)

T.O.T. *(Time on Target)*
Cell-based tests to predict and speed up the progress of Oncodesign's programs towards their therapeutic indication

PREDICT® – Inflammatory Diseases

Autoimmunity

Colitis |
Rheumatoid Arthritis |
Multiple sclerosis |
Type I Diabetes

Skin

Psoriasis |
Atopic Dermatitis |
Itch |
Scleroderma |
Acne |

Liver

Acute Liver Injury |
Cholestasis |
Liver Fibrosis |

Kidney

Acute Kidney Injury |
Diabetic Nephropathy |
Kidney Fibrosis UUO |

Lung

Bronchiolitis |
Asthma |
Lung Fibrosis |

Low grade inflammation

Dyslipidemia |
Atherosclerosis |
Obesity |
Hypertension |
Type 2 Diabetes |

Septic shock

LPS | *Feces* | *CLP* |

❷ Syngeneic tumor models

Syngeneic tumor models

Murine models

Bladder CA	MBT-2
Breast CA	EMT6 | 4T1 (M)
Colon ACA	C26
Colon CA	C38 | C51 | CT26 (M) MC38
Kidney CA	Renca (M)
Melanoma	B16-F10 (M)
Mesothelioma	AB12
Liver CA	Hepa1-6
Lung CA	LLC1 (M)
Pancreas ACA	Pan02
AML	C1498
Leukemia	P388 | P388/ADR | L2110 | L2110/CDDP
Lymphoma	A20
Plasmacytoma	MPC-11

Rat models

Bladder CA	NBT-II | AY27
Colon ACA	PROb | REGb
Glioma	C6 | GV1A1
Gliosarcoma	GS-9L
Prostate CA	MAT-LyLu (M) | R3327-AT3 | R3327H

An extensive panel of well characterized syngeneic models in both mouse and rat

NEW ONGOING

GL261 Q3 2018

Rat syngeneic models : FAT-7, MAT B III, McA-RH7777

Mouse GvHD model

CA: carcinoma ACA: Adenocarcinoma (M) : develop metastasis

Checkpoint inhibitors

Model		CTLA-4		PD-1		PD-L1		OX40		4-1BB		GITR		Tim3	
		n (study)	T/C (median)	n (study)	T/C (median)	n (study)	T/C (median)	n (study)	T/C (median)	n (study)	T/C (median)	n (study)	T/C (median)	n (study)	T/C (median)
4T1	OT	10	79	16	97	3	104	1	121	1	65				
A20	SC	2	53	5	30	1	59								
B16-F10	SC	3	100	4	133	3	91								
C38	SC	3	0	4	27										
CT26	SC	13	22	26	70	10	66	2	25	2	15	6	16	1	80
EMT6	OT			2	75										
EMT6	SC	12	4	34	52	3	68	3	20	6	4	2	32	2	65
HEPA1-6**	OT	2	27	1	191					1	0				
LLC	SC	3	97	4	111	1	88	1	108						
MBT2**	OT	2	285	7	148										
MBT2	SC	2	66	8	72	4	59	2	69						
PAN02	SC	1	5												
Renca**	OT			2	146										
Renca	SC			3	62			1	65						
TC1	SC			2	92										

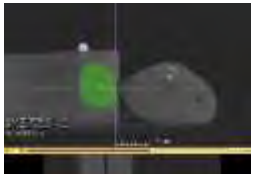
	T/C < 42%
	42% < T/C < 80%
	T/C > 80%

** survival
n: number of study used to calculate optimum T/C (%) values

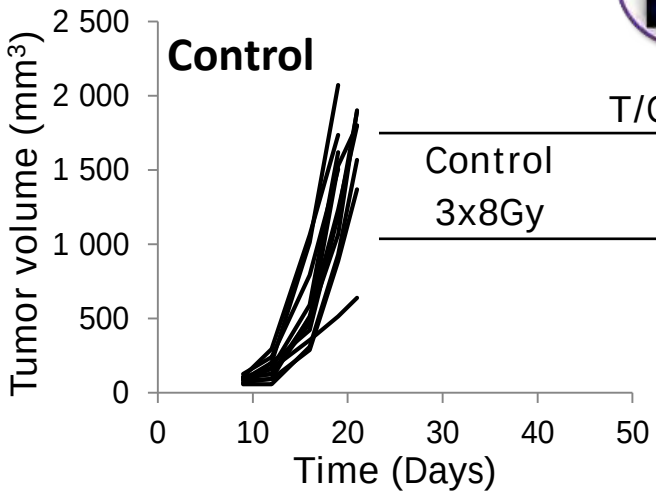
Chemotherapy – Radiotherapy response

Name	Site	Type	Strain	5-fluorouracil	cisplatin	oxaliplatin	cyclophosphamide	docetaxel	paclitaxel	doxorubicin	gemcitabine	irinotecan	radiotherapy
4T1	OT	Breast	Balb/c						x				x
B16-F10	IV	Melanoma	C57Bl/6				x		x				
B16-F10	SC	Melanoma	C57Bl/6						x	x			
C26	SC	Colon	Balb/c		x	x						x	
C38	SC	Colon	C57Bl/6			x						x	x
C51	SC	Colon	Balb/c			x						x	
CT26	SC	Colon	Balb/c	x								x	x
EMT6	SC	Breast	Balb/c					x	x	x			x
HEPA1-6	OT	Liver	C57Bl/6							x			
L1210	IP	Leukemia	DBA/2		x	x				x			
L1210/CDDP	IP	Leukemia	DBA/2		x	x							
LLC	IV	Lung	C57Bl/6				x						
LLC	SC	Lung	C57Bl/6				x						
MBT2	OT	Bladder	C3H					x			x		
Renca	OT	Kidney	Balb/c		x				x		x		
Renca	SC	Kidney	Balb/c										x

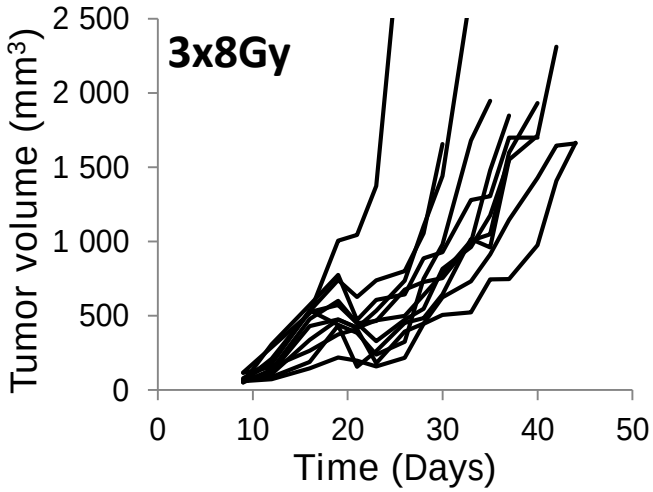
Tumor localized and image guided radiotherapy



Data and Images courtesy by Céline Mirjolet-Didelot, PhD, Radiobiologist, CGFL, Dijon

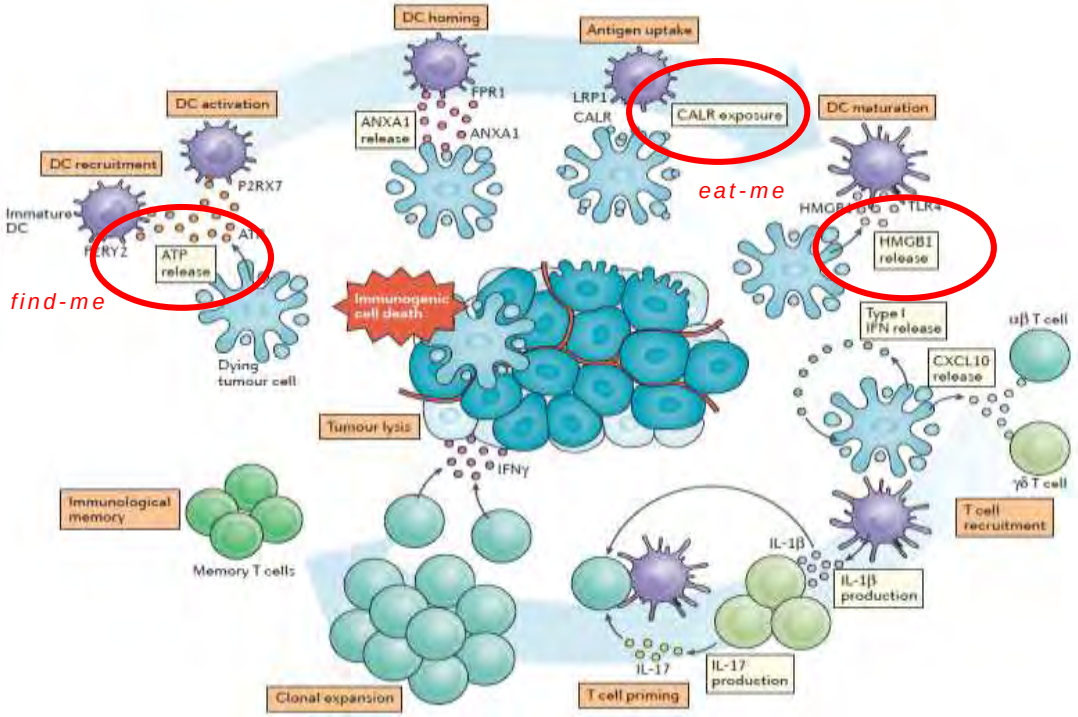


	T/C % (D21)
Control	100
3x8Gy	23



Mice were SC injected with CT-26 murine colon tumor cells at D0. Mice were randomized based on tumor volume at D12 and treated with imaged guide 3D radiotherapy at 8Gy for three consecutive days.

Immunogenic Cell Death (ICD)



DAMPs (CRT, HMGB1 and ATP) released during ICD are recruiting and activating immune cells (DC, moncoytes, Tcells) for the reconnaissance of tumoral (neo)-antigens.
Galuzzi et al, Nature Reviews Immunology 2017 17, 97–111

So far, 3 damage-associated molecular patterns have been attributed a key role in the immunogenic potential of virtually all ICD inducers:

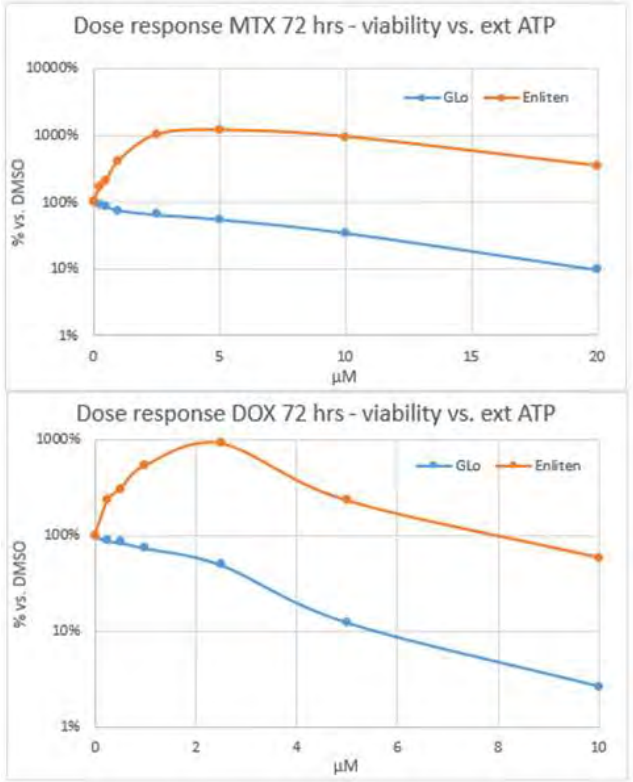
- ATP,
- the endoplasmic reticulum (ER) chaperone calreticulin (CALR) and,
- HMGB1

NEW

- Our screening platform:
  - 3 Cell lines
    - Human: U-2 OS and MDA-MB-231
    - Mouse: Hepa1-6
  - Positive controls
    - Doxorubicin
    - Mitoxantrone

Two reference drugs increase extracellular ATP amount in the absence of cell toxicity

Dose response in Hepa 1-6 cells



Doxorubicin (Doxo) and MTX (Mitoxantrone) increase extracellular ATP content (ENLITEN® Promega) at non-toxic doses determined by CellTiter-Glo® (Promega) in 3 cell lines

	U-2 OS		MDA-MB-231		HEPA 1-6	
	Viability	ext ATP	Viability	ext ATP	Viability	ext ATP
MTX 0.2 µM	84%	757%	84%	786%	92%	237%
Dox 0.2 µM	90%	647%	94%	297%	95%	254%

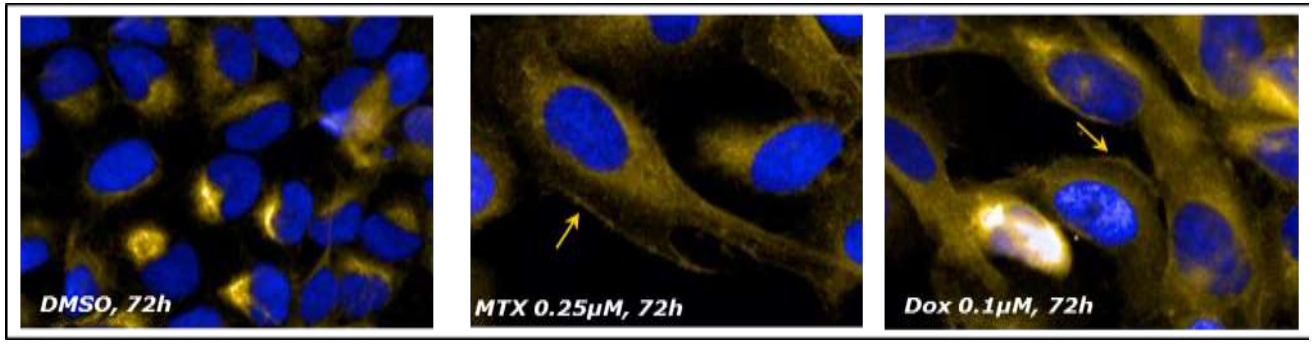
Results expressed as a percentage vs. DMSO normalized at 100 %

MTX (Mitoxantrone) increase HMGB1 in 2 cell lines at non toxic concentration.

	MDA-MB-231	HEPA 1-6
	HMGB1	HMGB1
MTX 0.5 µM	187%	191%

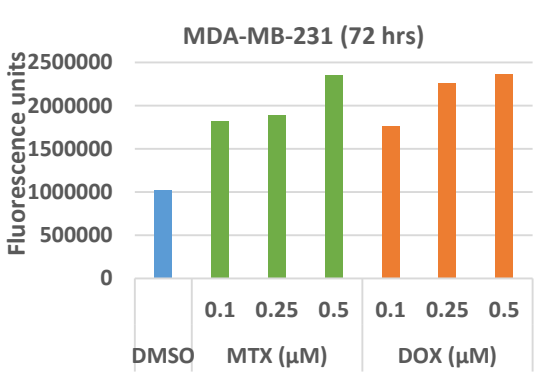
Results expressed as a percentage vs. DMSO normalized at 100 %

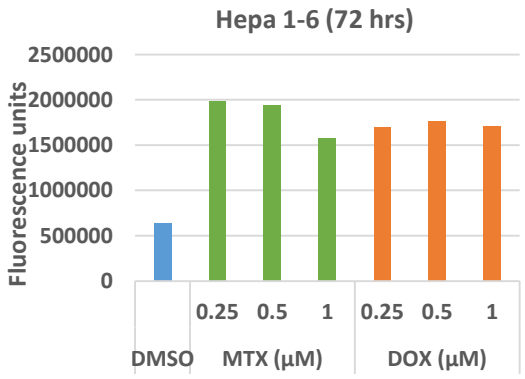
Two reference drugs increase extracellular plasma membrane calreticulin amount in the absence of cell toxicity

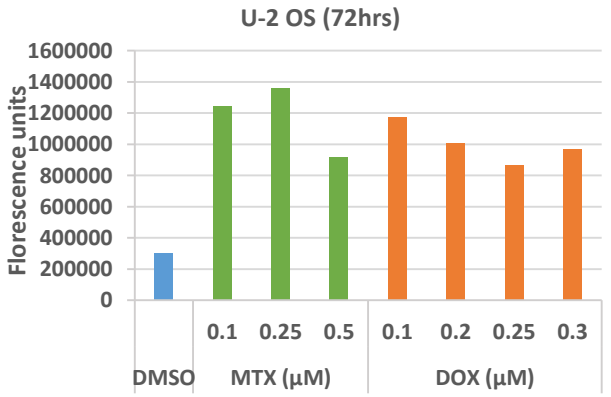


Calreticulin membrane expression is indicated by the arrows in the drug-treated samples.

Drugs were incubated at the indicated doses (µM) for 72 hrs on murine Hepa 1-6 cells and human U-2 OS and MDA-MB-231 cells. Calreticulin membrane intensity fluorescence is detected and quantified using a high content Operetta reader.

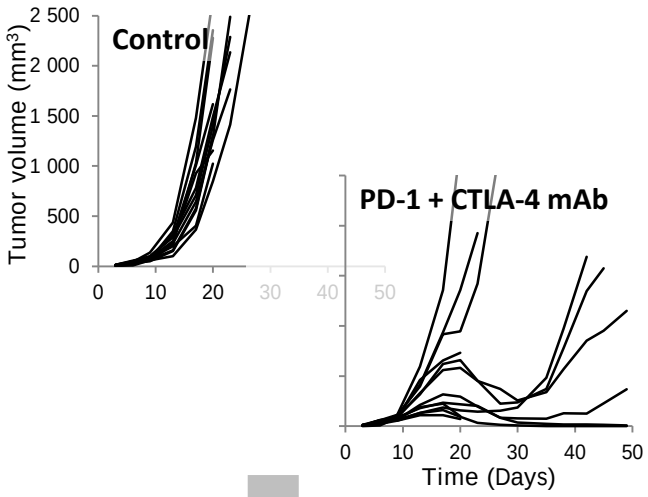




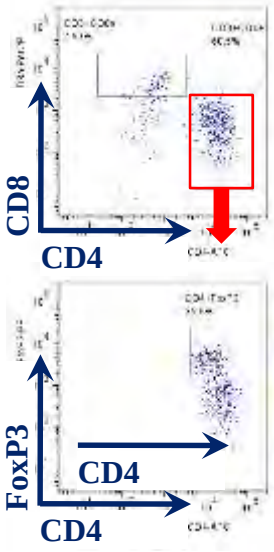


Readouts in murine models

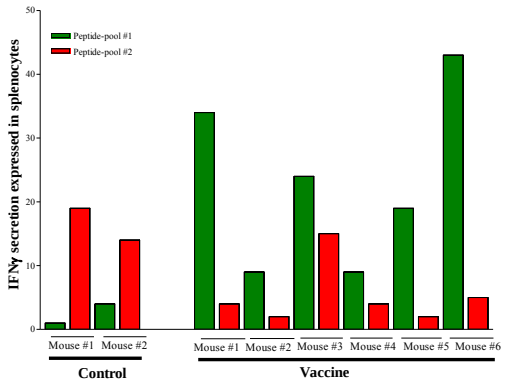
Tumor growth curves



Flow Cytometry

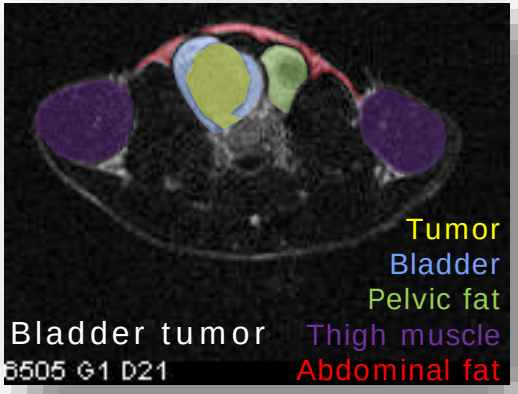


Functional assays

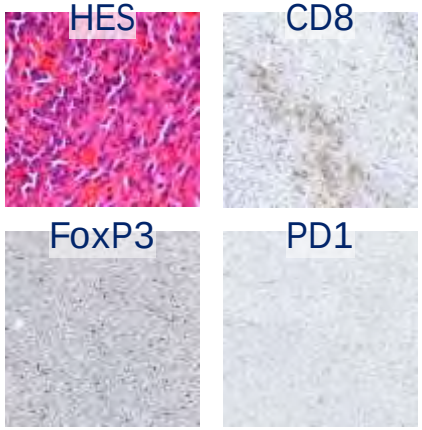


IFNγ secretion using ELISpot assay

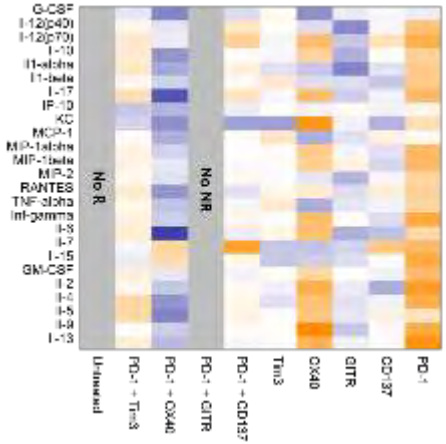
Imaging



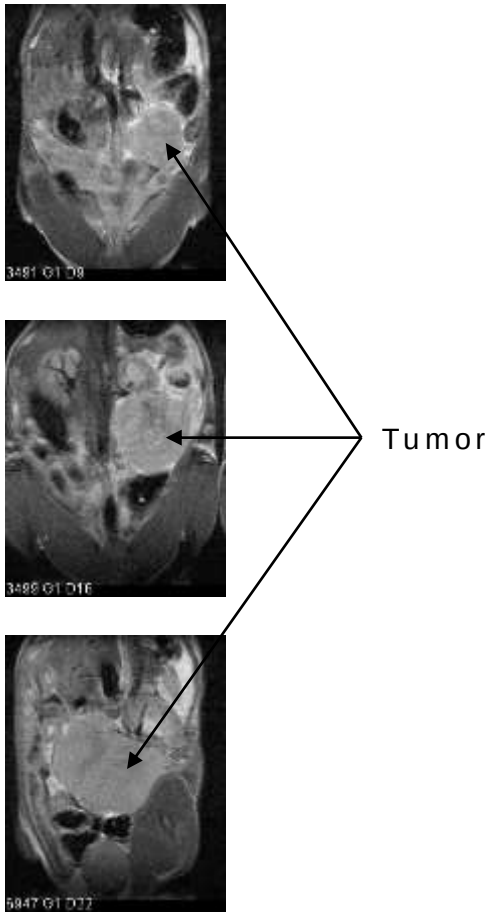
IHC

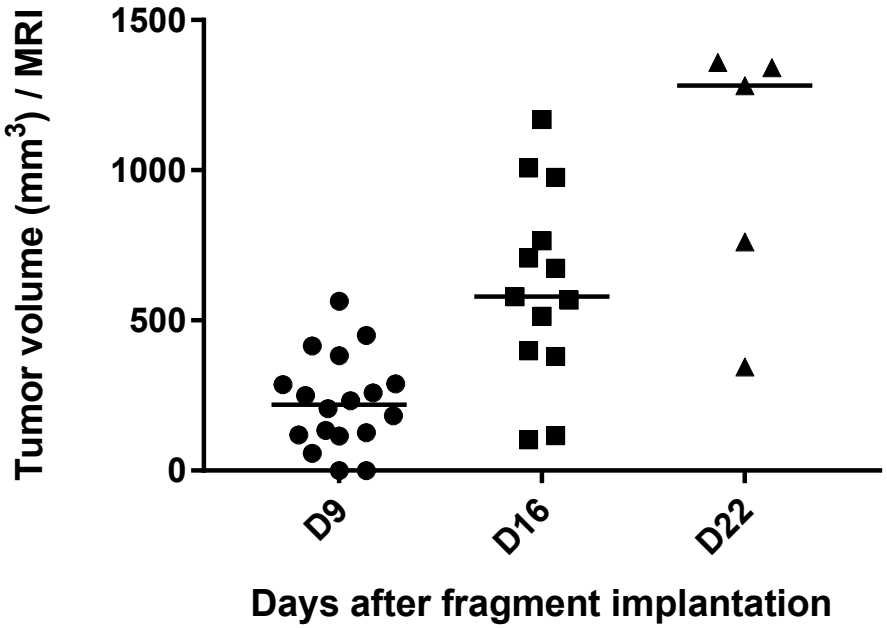


Cytokine profile



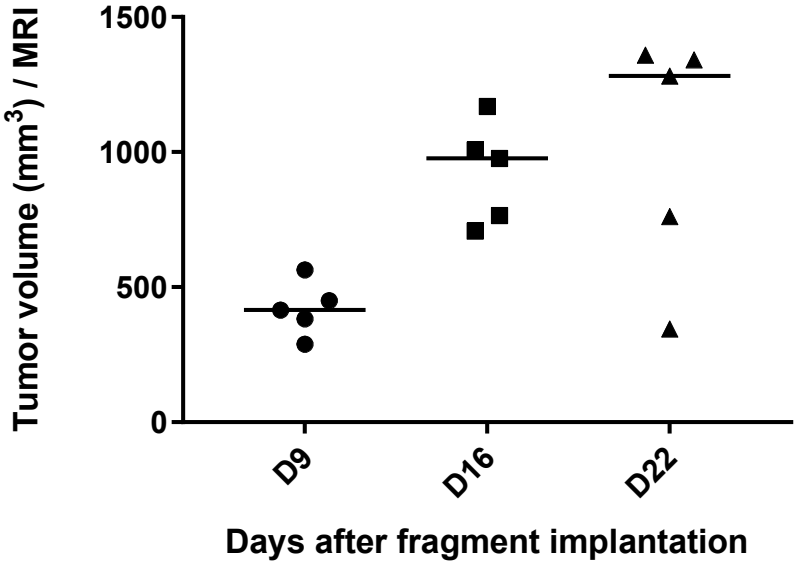
Tumor growth PAN02 OT tumors in C57BL/6 mice
Assessment of tumor volume by MRI

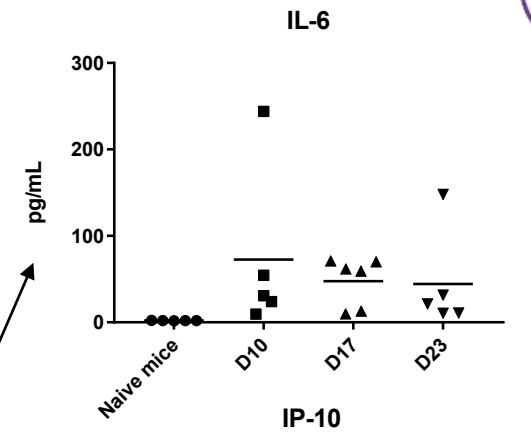


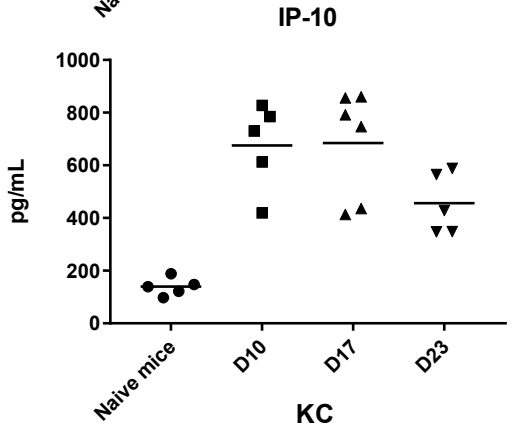


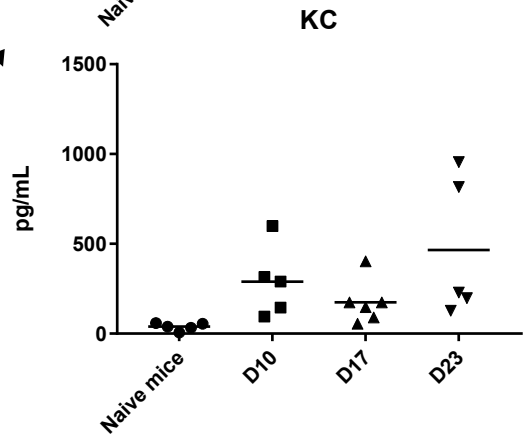
N=18 mice.
Tumor fragment implanted OT at D0
The horizontal bar indicates the median of the group

The seric inflammatory IL-6 / IP-10 and KC cytokines linked to PAN02 OT growth









Mice evaluated by MRI at D9/D16 & D22 were sacrificed the next day (i.e, D10, D17 and D23) to collect tumor (→ evaluation of immune infiltrates by flow cytometry) and blood (→ cytokine assays)

The horizontal bar indicates the median of the group

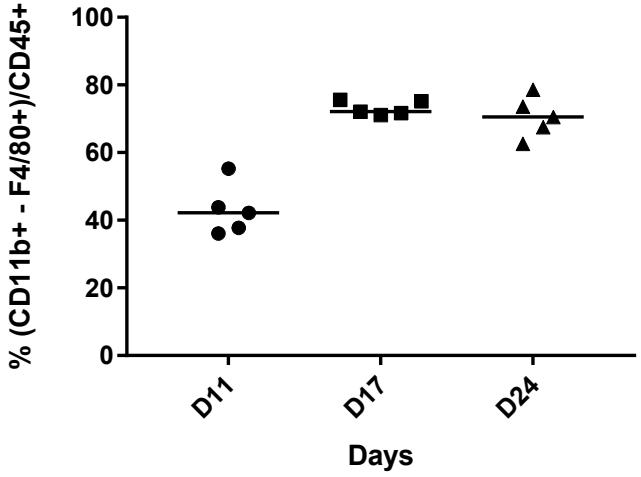
Immune infiltrate phenotyping

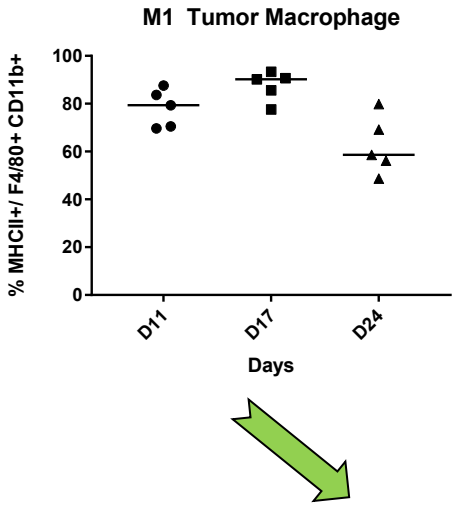
- *Immune cell phenotyping using Flow Cytometry*
  - *Panels up to 10 colors*

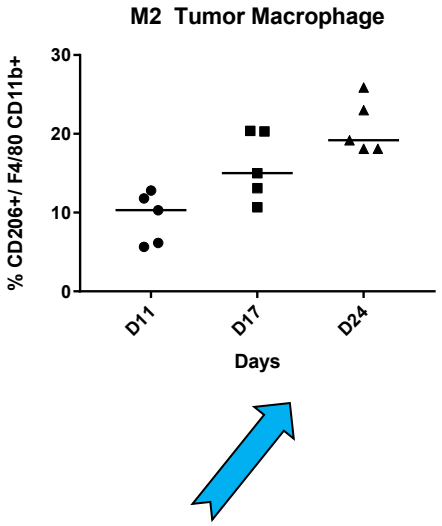
Populations	Markers
Teff	CD45+ CD3+ CD4- CD8+
Treg	CD45+ CD3+ CD4+ CD8- FoxP3+
Cytolytic Teff	CD45+ CD3+ CD8+ TNF-α Perforin Granzyme B
Total MDSCs	CD45+ CD3- CD11b+ Gr1+
M-MDSCs	CD45+ CD3- CD11b+ Gr1+ Ly6G- Ly6C+ (iNOS, Arg1)
G-MDSCs	CD45+ CD3- CD11b+ Gr1+ Ly6G+ Ly6C- (iNOS, Arg1)
Total TAMs	CD45+ CD3- CD11b+ Gr1-
M1 TAM	CD45+ CD3- CD11b+ Gr1- F4/80+ CD206- MHCII ^{hi}
M2 TAM	CD45+ CD3- CD11b+ Gr1- F4/80+ CD206+ MHCII ^{low}
NK - C57BL/6	CD45+ CD3- NK1.1+ NKp46+
NK - BALB/c	CD45+ CD3- CD49+ NKp46+

A M1/M2 macrophage switch in growing PAN02 OT tumors

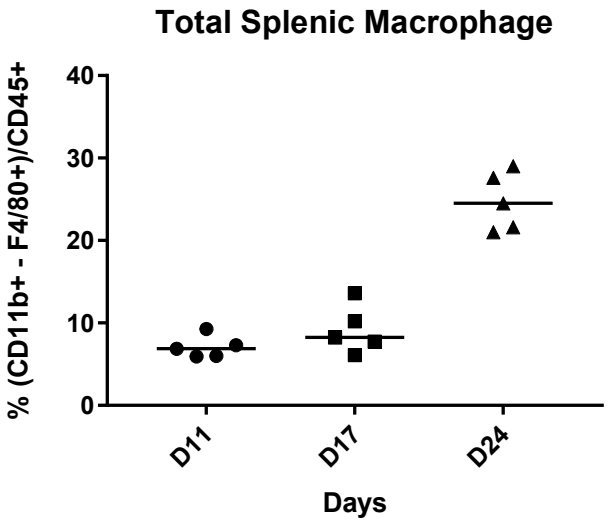
TUMOR

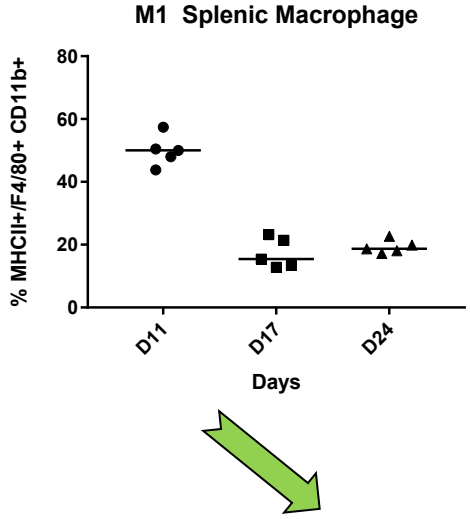


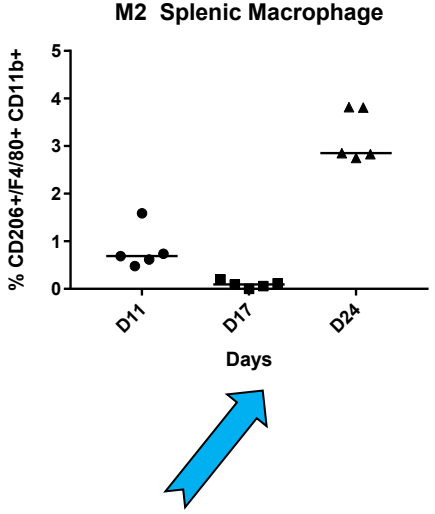




SPLEEN

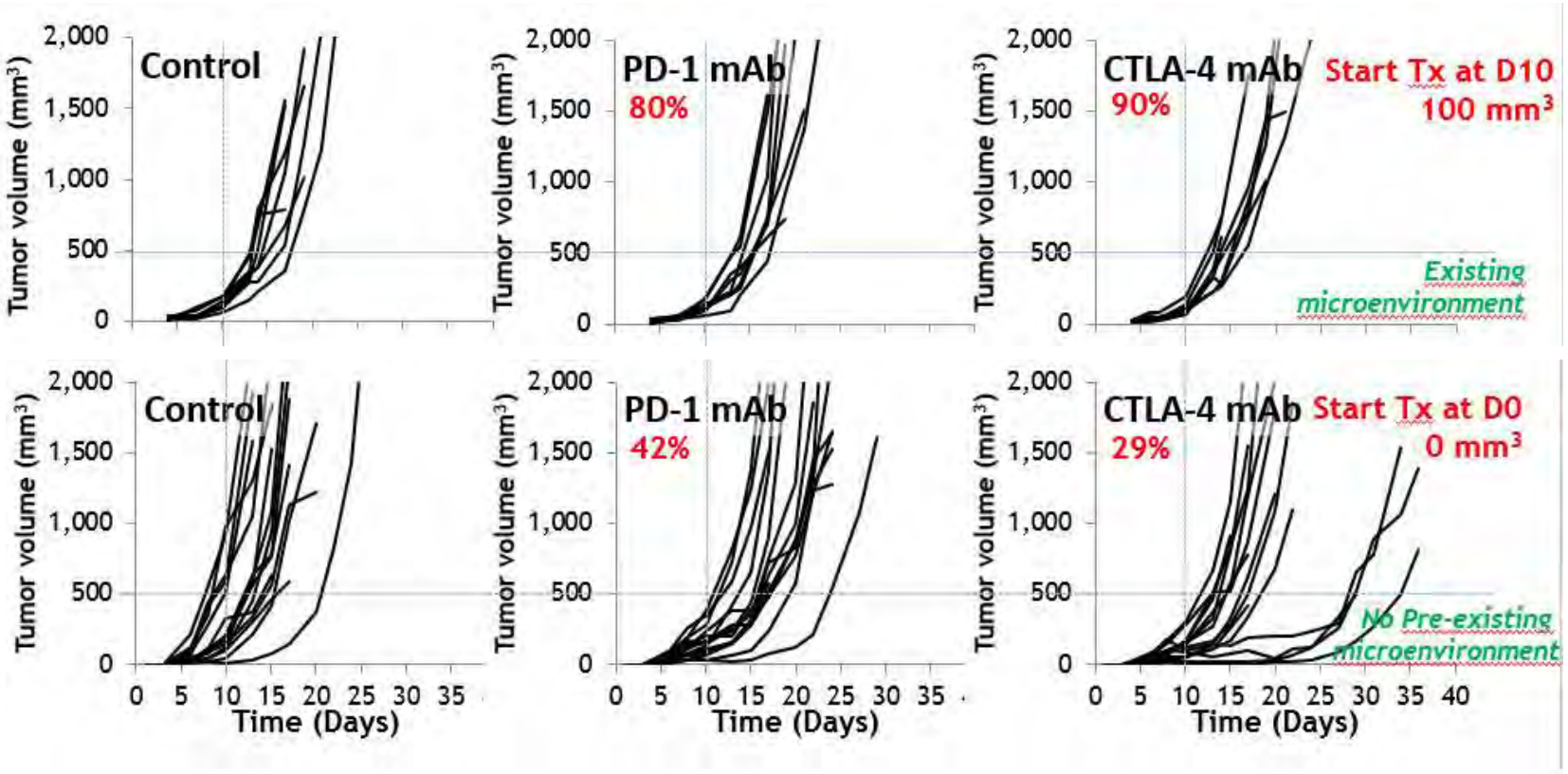






B16-F10 melanoma model

- Immune checkpoint inhibitor efficacy depends on tumor volume at treatment start!

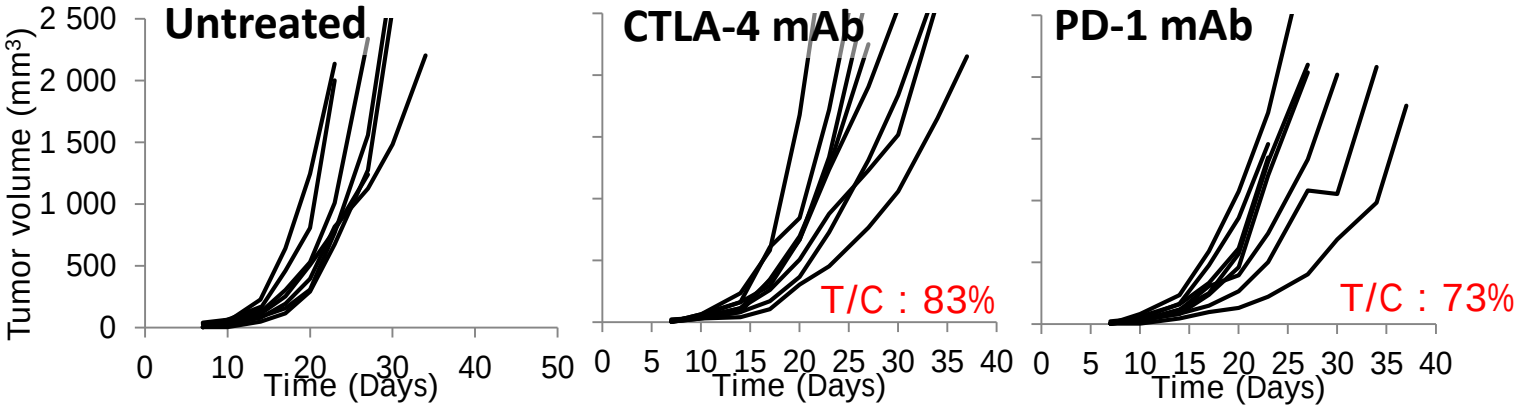


Mice were SC injected with B16-F10 mouse tumor cells at D_0. Mice were randomized based on body weight or TV and treated IP with mAb against CTLA-4 (clone 9H10) at 10 mg/kg (TWx2) or against PD-1 (clone RPMI-14) at 10 mg/kg/inj (TWx2).

MBT-2 Bladder carcinoma model

- Immune checkpoint inhibitor efficacy depends on tumor model: SC vs OT model!

❶



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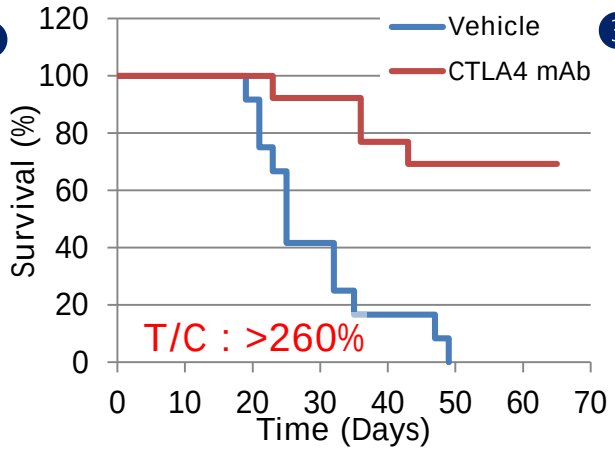

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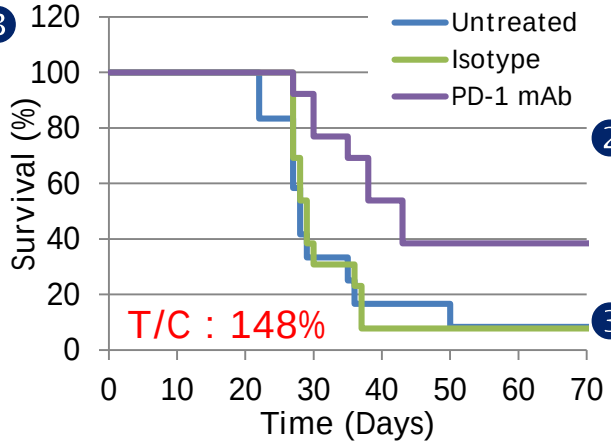
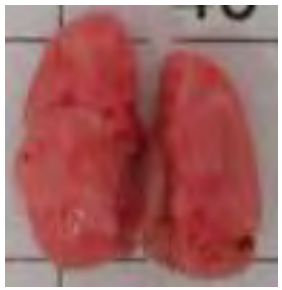


❶ SC injection at D0
Randomization on TV at D14
IP injection at 10 mg/kg/inj (TWx2)
- mAb against CTLA-4 (clone 9H10)
- mAb against PD-1 (clone RMP1-14)

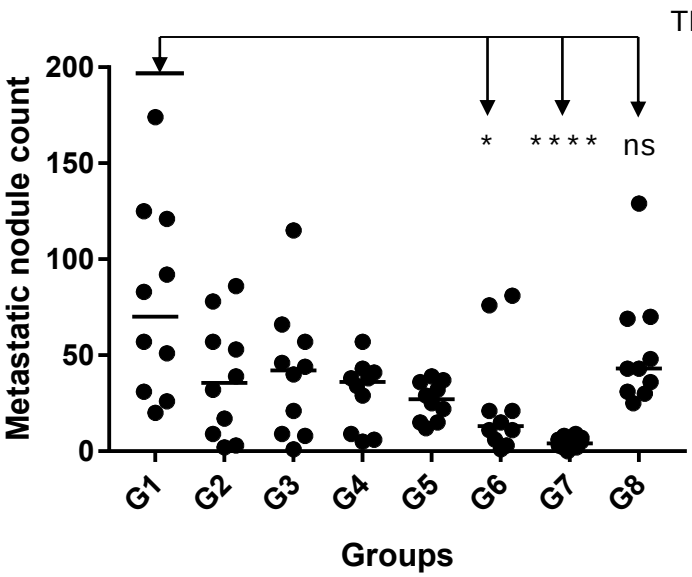
❷ OT injection at D0
Randomization on BW at D5
IP injection at 10 mg/kg/inj (TWx2)
- mAb against CTLA-4 (clone 9H10)

❸ OT injection at D0
Randomization on BW at D3
IP injection at 10 mg/kg/inj (TWx2)
- mAb anti-PD-1 (clone RMP1-14)
- Isotype (clone 2A3)

Metastasis detection – IV B16-F10 model
Improved detection of metastasis using qPCR of specific melanoma genes

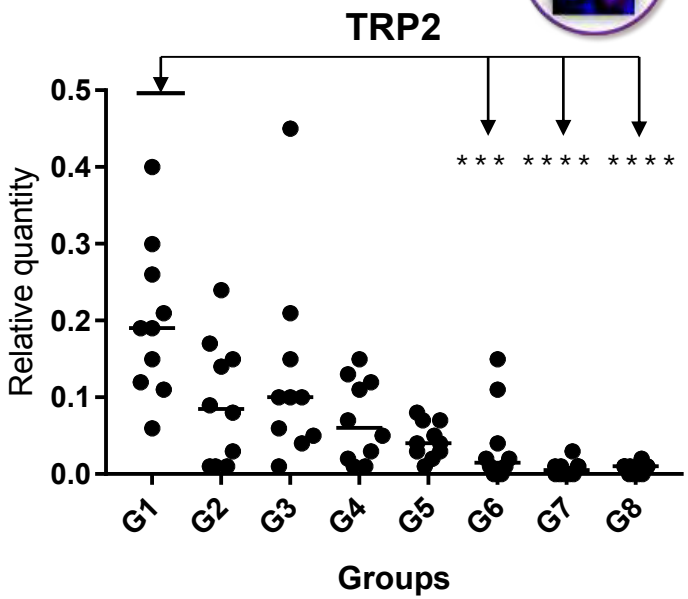


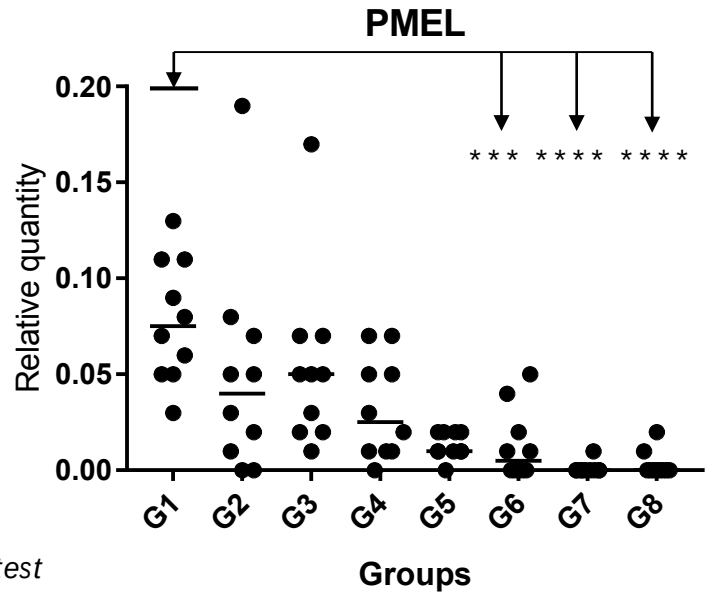
Met counts : 174/G1 36/G8



TRP2 mRNA

PMEL mRNA



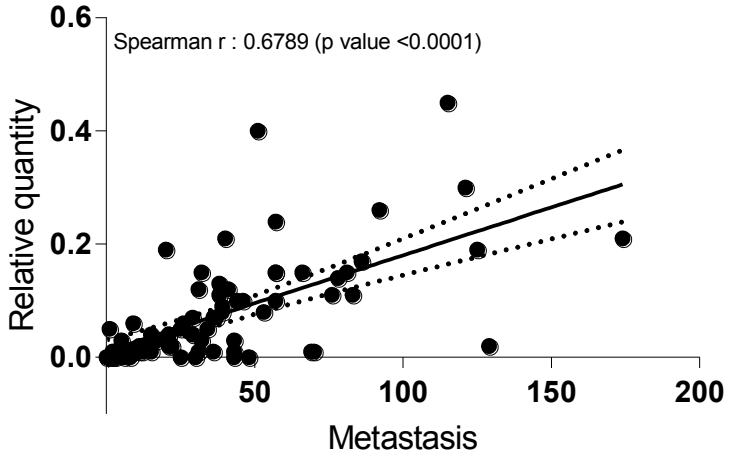


G1 = Vehicle-treated group
G8 = Cyclophosphamide-treated group (Positive control)

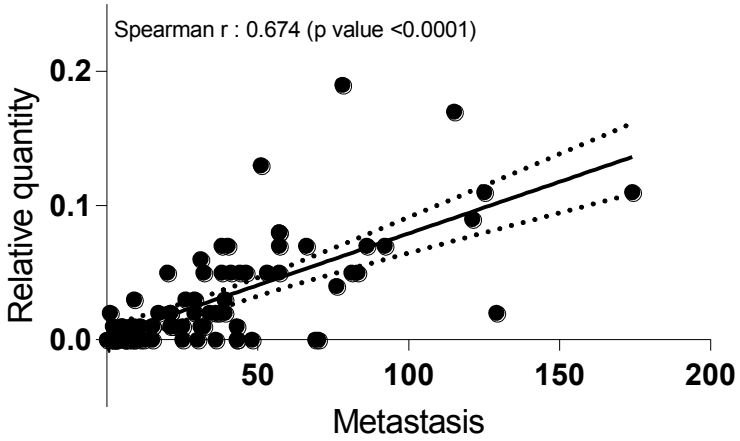
**p<0.05, *** p<0.001, **** p<0.0001 Dunn's multiple comparisons test*

Metastasis detection – IV B16-F10 model : singleplex Q-PCR for quantification of B16-F10 melanoma cells in lungs

TRP2 *vs*. Metastasis



PMEL *vs*. Metastasis



❸ PDX models

PDX models at Oncodesign

IMODI
INNOVATIVE MODELS INITIATIVE AGAINST CANCER

CREMEC

Published OnlineFirst on July 23, 2012; DOI: 10.1158/1078-0432.CCR-12-0372
Clinical Cancer Research
Cancer Therapy: Preclinical

Characterization of a Large Panel of Patient-Derived Tumor Xenografts Representing the Clinical Heterogeneity of Human Colorectal Cancer

Sylvia Julien[1], Ana Merino-Trigo[2], Ludovic Lacroix[3], Marc Pocard[4], Diane Goéré[5], Pascale Mariani[6], Sophie Landron[3], Ludovic Bigot[1], Fyrbe Nemati[1], Peggy Dartigues[1], Louis-Bastien Weiswald[1], Denis Lantuéjoul[7], Loïc Morgand[8], Emmanuel Rhem[1], Patrick Gonin[9], Virginie Dorigès-Morel[1,7], Bastien Job[1], Philippe Dessen[10], Alain Bruno[1], Alain Pierré[1], Hugues De Thé[11], Hany Soliman[12], Manuel Nunes[13], Guillaume Lardier[2], Loreley Calvet[2], Brigitte Dennes[1], Grégoire Prévost[1], Patricia Vagnaud[1], Sergio Roman-Roman[3], Olivier Duchamp[3], and Cyril Bertret[3]

Not only numbers, but an extensive characterization and knowledge of our models, both the original tumor and PDX:

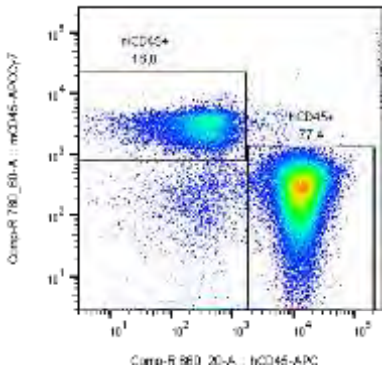
* histology
* CGH
* Genome sequencing
* Transcriptome
* Pharmacology - 4 SOC
* Gut microbiota of the host

	CR-IGR-0023M	CR-IC-0004M	CR-IC-0007M	CR-IGR-0007P	CR-IGR-0025P	CR-LRB-0010P	CR-LRB-0011M	CR-LRB-0013P
							60%	80%
TP53 62%								
APC 53%								
KRAS 45%								
PIK3CA 10%								
FBXW7 8%								
BRAF 5%								
CTNNB1 3%								
EGFR 2%								
AKT1 0%								
MSI status	MSS	MSS	MSS	MSS	MSS	MSS	MSS	MSS
Xenograft								
CGH Analysis								
Other								
5-FU	+	-	-	-	-	-	+	+
I-OHP	-	-	-	-	-	-	-	-
CPT-11	+	+	++	+	+	++	+++	
CETUXIMAB	+	++	+++	+	-	-	-	-

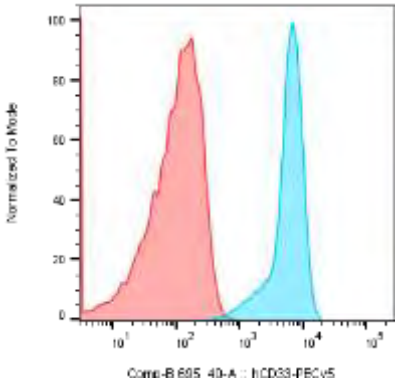
ERCC1-A138T

AML PDX (IM-LAM-032) - Phenotyping study

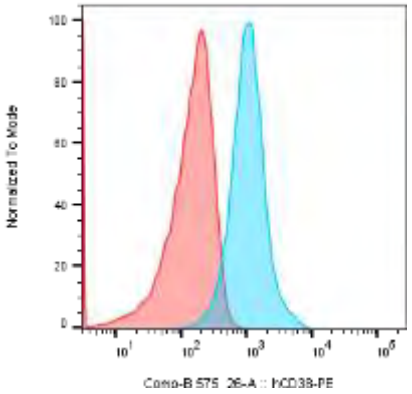
Mouse id: 61656
Group: untreated
Organ: Bone Marrow



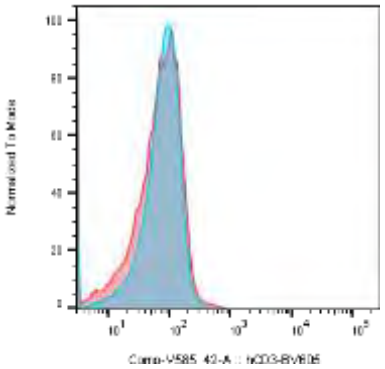
CD33



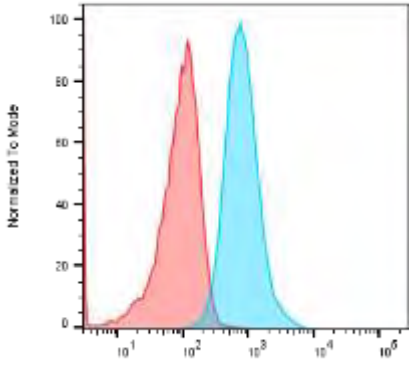
CD38



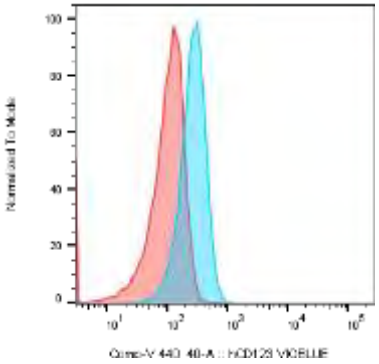
CD3



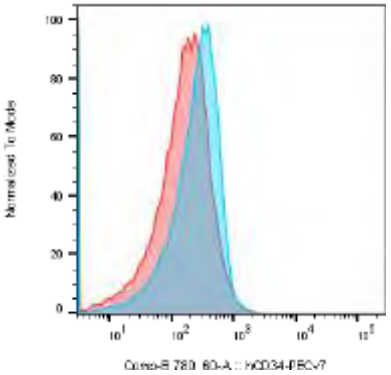
CD44



CD123

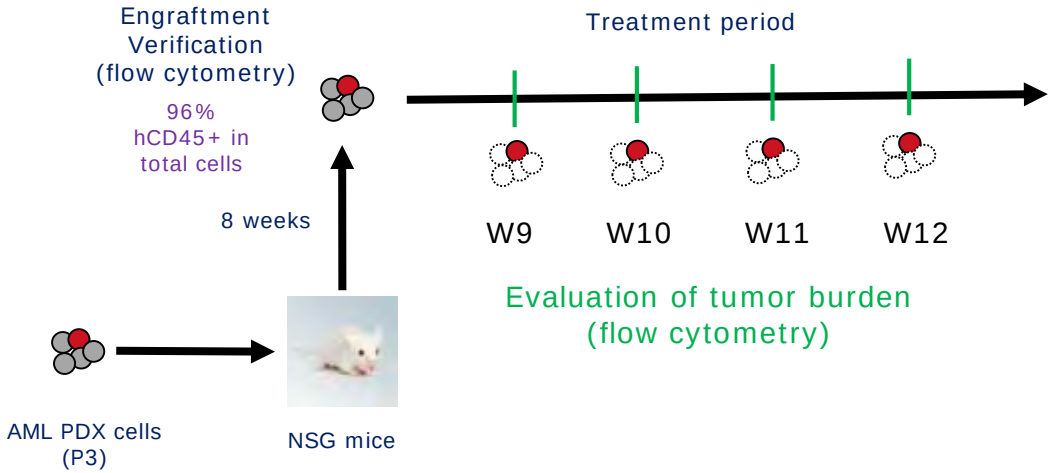


CD34

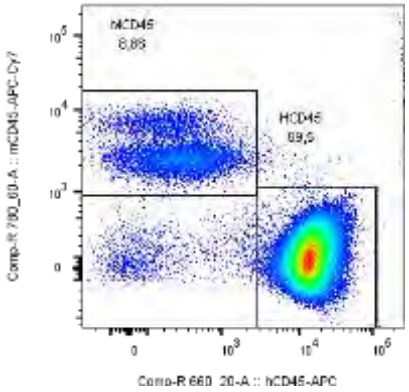


IMODI
INNOVATIVE MODELS INITIATIVE AGAINST CANCER

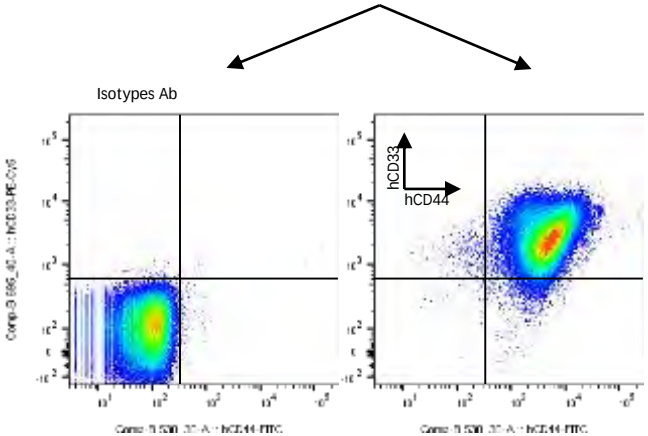
AML PDX (IM-LAM-032) - Pharmacology study



Mouse id: 63729
Group: untreated
Organ: blood



Group	No animals	Treatment	Dose (mg/kg/adm)	Adm. Route	Treatment schedule
1	6	Not treated	-	-	-
2	6	Cytarabine (Ara-C)	60	IP	Q1Dx5
3	6	Idarubicine (Ida)	0,3	IV	Q2Dx3
4	6	Quizartinib (AC220)	10	PO	(Q1Dx3)x4

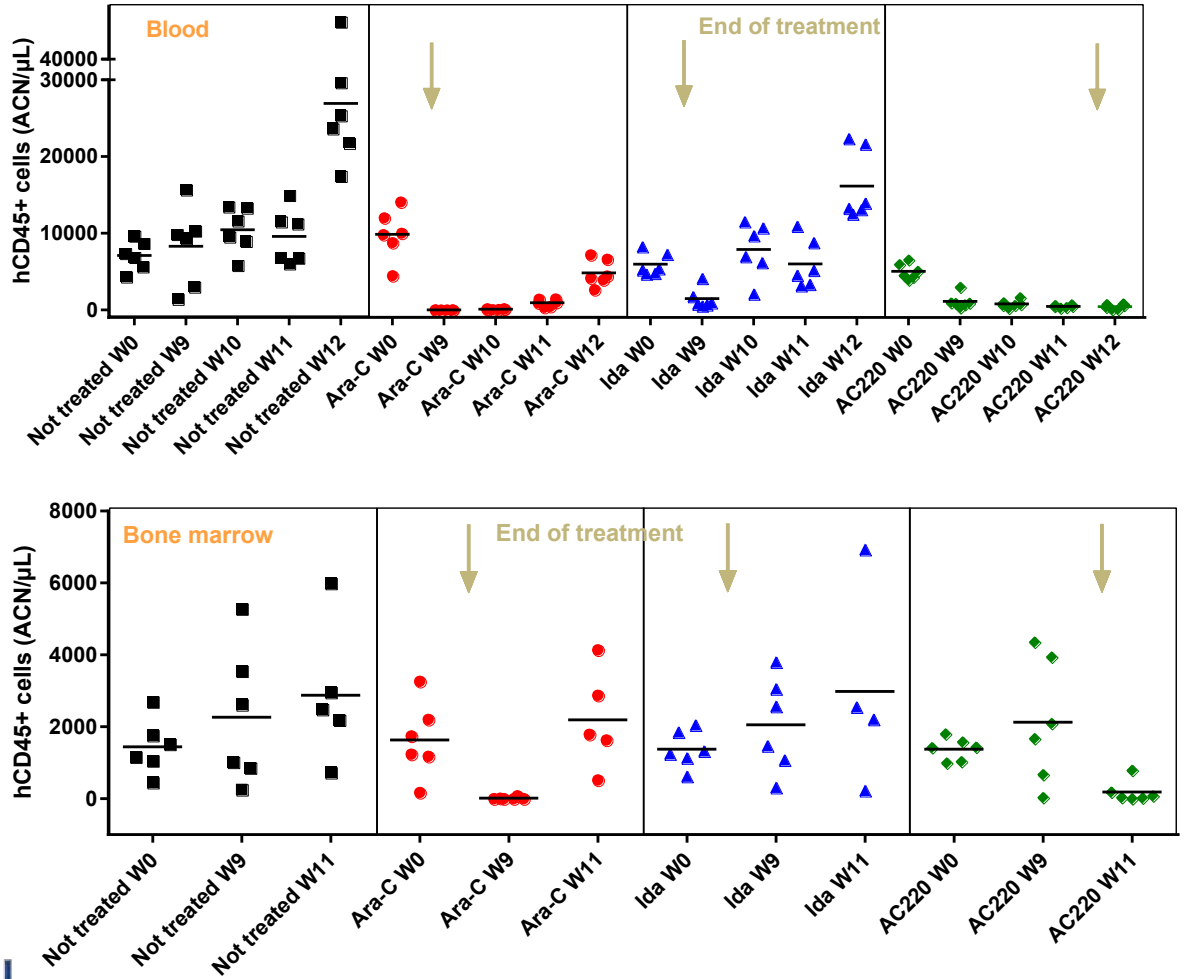


IM-LAM-032 PDX : FLT3, NPM1, DNMT3a mutated

IMODI
INNOVATIVE MODELS INITIATIVE AGAINST CANCER

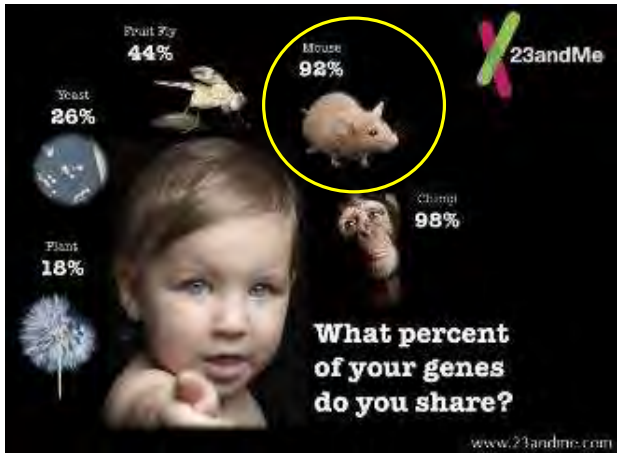
AML PDX (IM-LAM-032) - Pharmacology study

- Evaluation of tumor burden reduction and time to relapse in blood and bone marrow from treated mice



4 Humanized mouse models

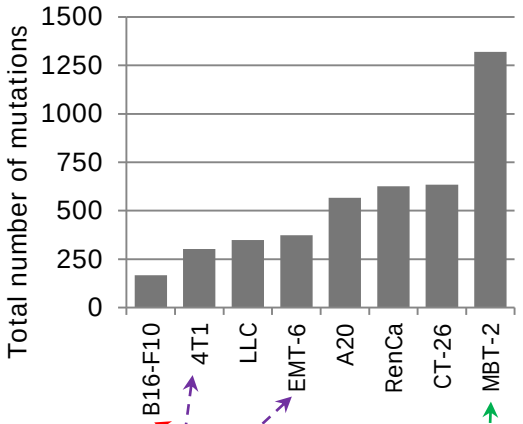
Why…



A Mouse is not a Human

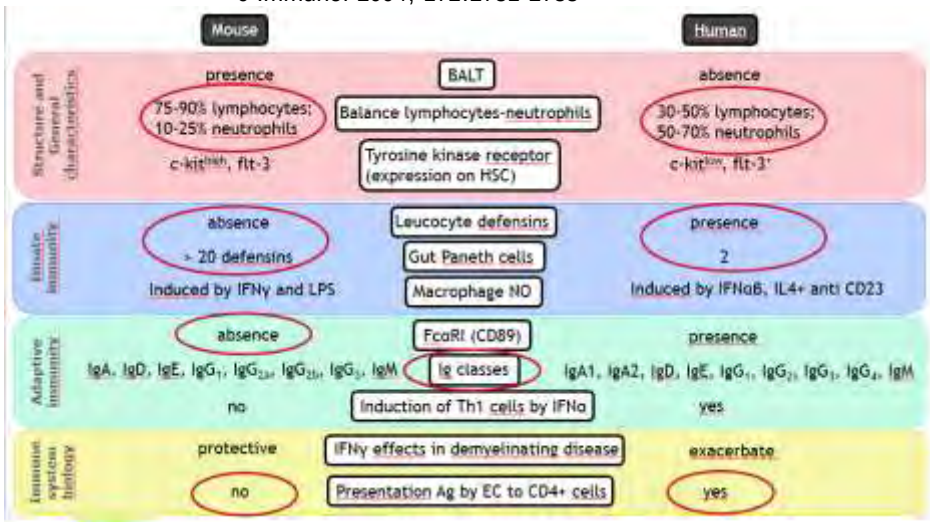
- size
- lifespan
- immune system (ecological niches)
- metabolic liver function
- …
- carcinogenesis mechanisms

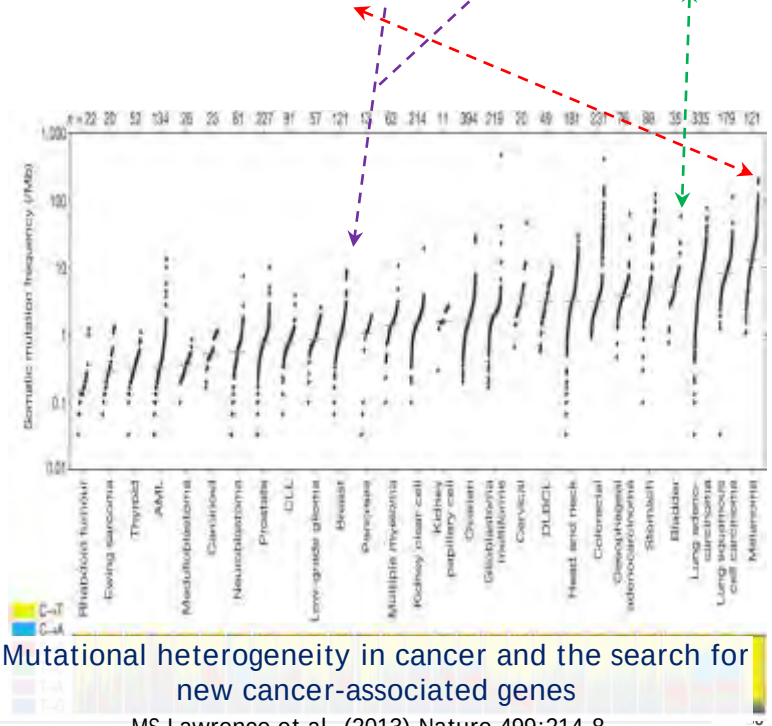
Tumor antigens



Of Mice and Not Men: Differences between Mouse and Human Immunology

Modified from Javier Mestas and Christopher C. W. Hughes,
J Immunol 2004; 172:2731-2738





Mutational heterogeneity in cancer and the search for new cancer-associated genes

MS Lawrence et al. (2013) Nature 499:214-8

Humanized mouse platform

➢ A comprehensive offer with solid experience and know-how

Immune system with hPBMCs	Immune system with hHSCs	Human liver	Human skin
Mouse Host SCID, NOD-SCID, SCID-Beige NSG, NOG	**Mouse Host** NSG, NSG-SGM3 NOG, NOG-IL2, NOG-IL15 NOG-EXL, BRGS	**Mouse Host** TK-NOG	**Mouse Host** SCID
1st study in 2002 at ODS	**1st study in 2008 at ODS**	**1st study in 2014 at ODS**	**1st study in 2011 at ODS**
● **Tumor free** - GvHD - Antigen recall response ● **Tumor bearing** - Ab targeting tumor antigen - Immune retargeting compounds - Engineered T cells - Immune checkpoint modulators	● **Tumor free** - Cytokine secretion assay ● **Tumor bearing** - Ab targeting tumor antigen - Engineered T cells - Immune checkpoint modulators	● **Tumor free** - Sorafenib PK/metabolism	● **Tumor free** - Vascular leak syndrome

Humanization of the immune system

- A wide scope of solid and heme tumor models
- PBMCs or purified/engineered T cells (IP, IV, SC mixed)

CDX (solid tumor)

Name	Histology	Injection
786-O	Kidney clear cell adenocarcinoma	SC
BT-474	Her2+ Breast ductal carcinoma	SC
CaSki	HPV16+ epidermoid cervical cancer	SC
FaDu	Head and Neck carcinoma	SC
HCT116	Colorectal carcinoma	SC
LoVo	Colorectal adenocarcinoma	SC
MCF-7	Breast adenocarcinoma	SC
MKN74	Stomach cancer	SC
NCI-N87	Gastric carcinoma (stomach)	SC
NIH:OVCAR-3	Ovarian adenocarcinoma	SC/IP

Immune system with hPBMCs

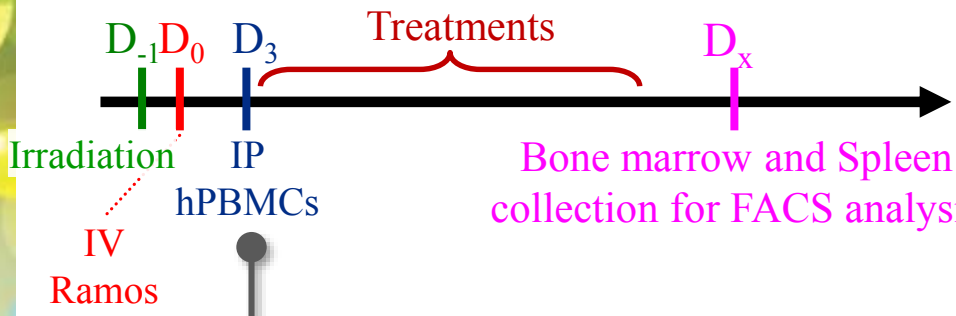
CDX (heme tumor)

Name	Histology	Injection
Daudi	Burkitt's lymphoma, B cells	IV
HL-60	Acute promyelocytic leukemia	SC
Jeko-1	Mantle Cell Lymphoma, B cells	IV
KARPAS-299	T-cell non-Hodgkin lymphoma	IV
MOLM13	Acute myeloid leukemia	IV
NCI-H929	Plasma cell myeloma	SC
Ramos	B cell lymphoma	IV

PDX

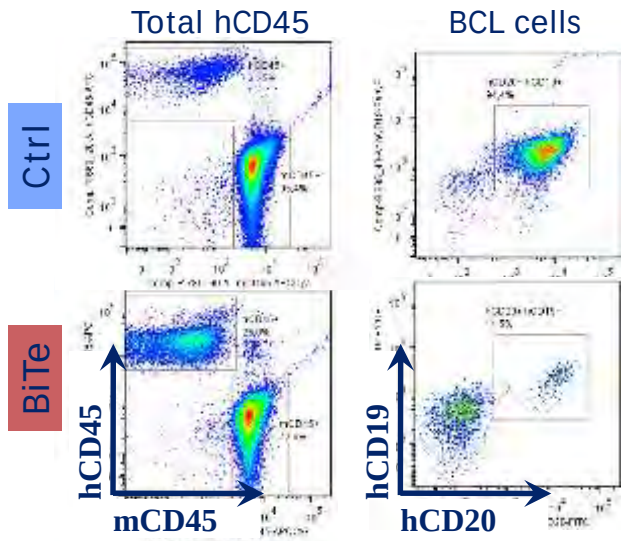
Name	Histology	Injection
LUN-NIC-001	NSCLC	SC
IM-BRE-044	Breast	SC
OD-BRE-0589	Breast	SC
IM-OVA-512	Ovary	SC
IM-OVA-535	Ovary	SC

Humanization of the immune system: BiTe Ab/Ramos B cell lymphoma model

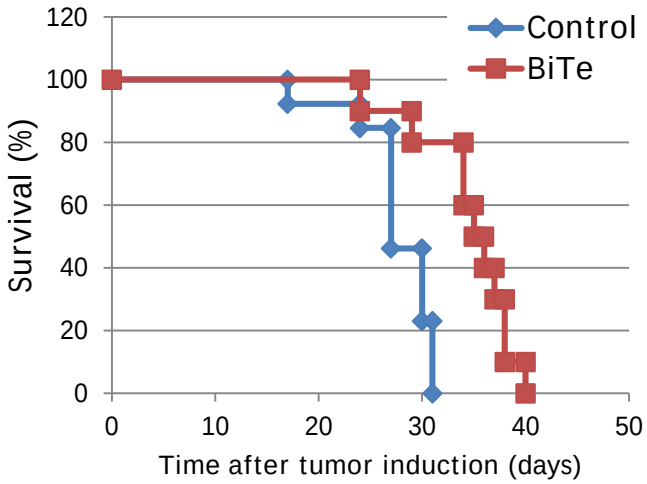


NOG + hPBMCs

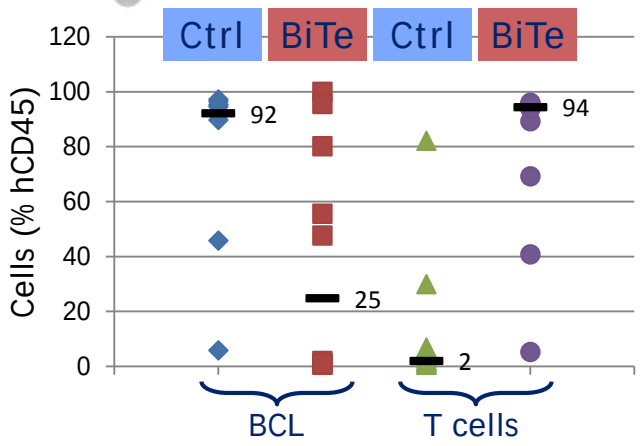
Tumor cell depletion



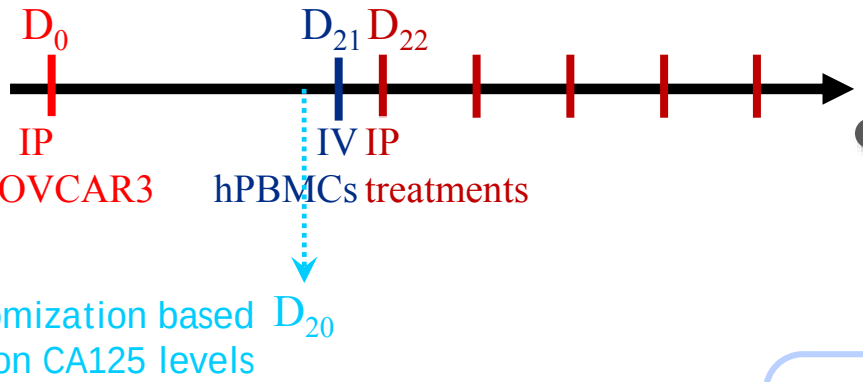
Survival increase



Immune cell recruitment

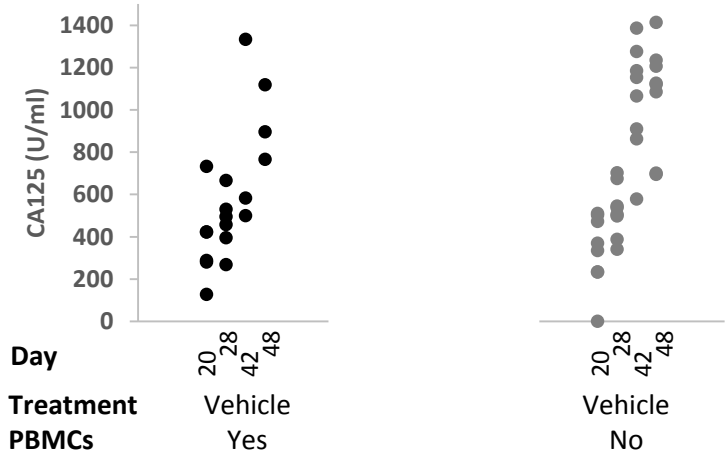


Humanized mouse platform: BiTe Ab/OVCAR3 adenocarcinoma model

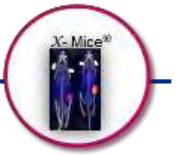


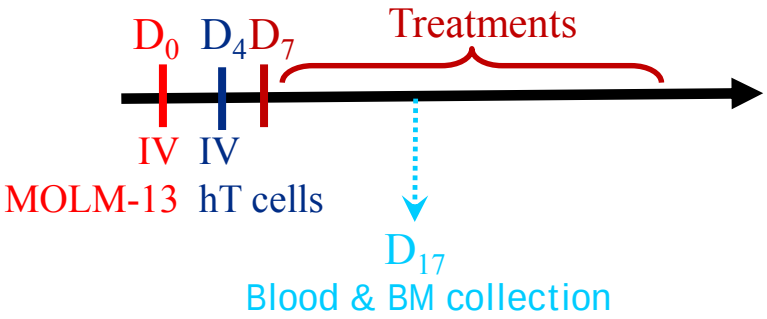
NOG + hPBMCs

- **Survival increase**
- **Tumor cell depletion**
- **Immune cell recruitment**
- **Circulating biomarker**



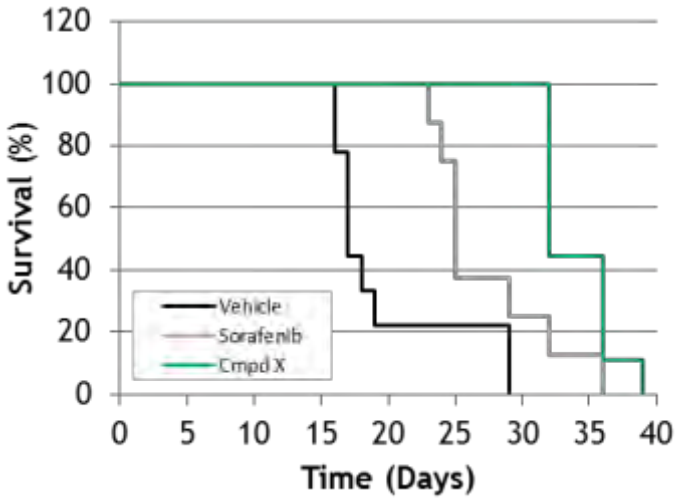
Humanized mouse platform: BiTe Ab/MOLM13 AML model



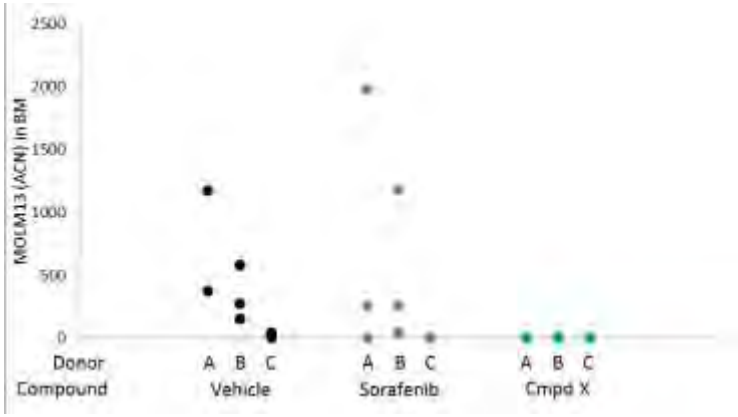


NOG + hT cells

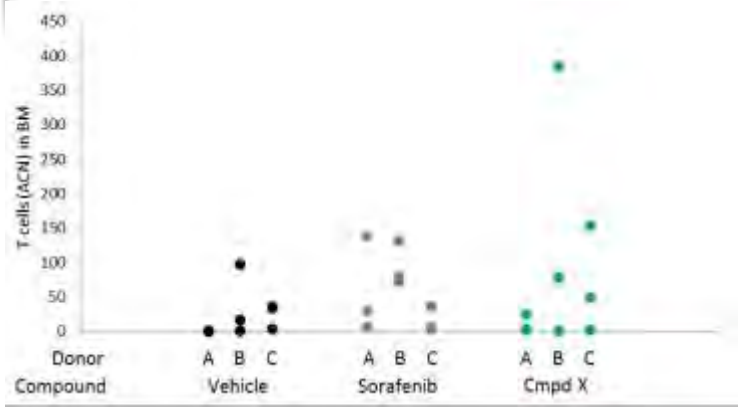
Survival increase



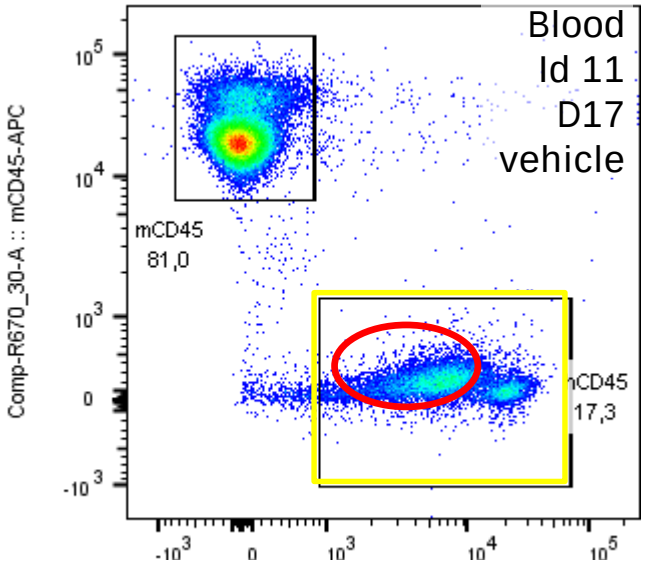
Tumor cell depletion

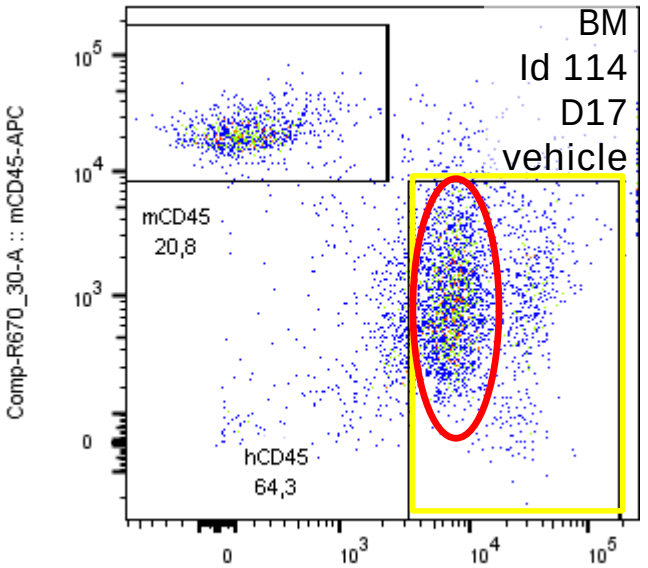


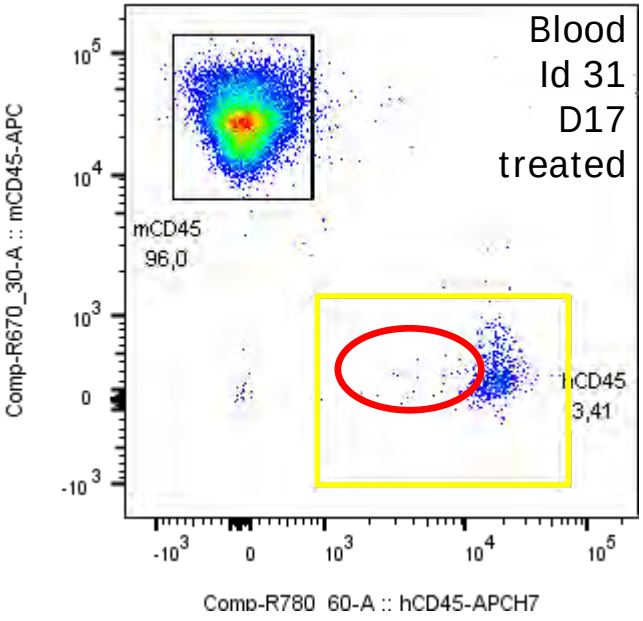
Immune cell recruitment

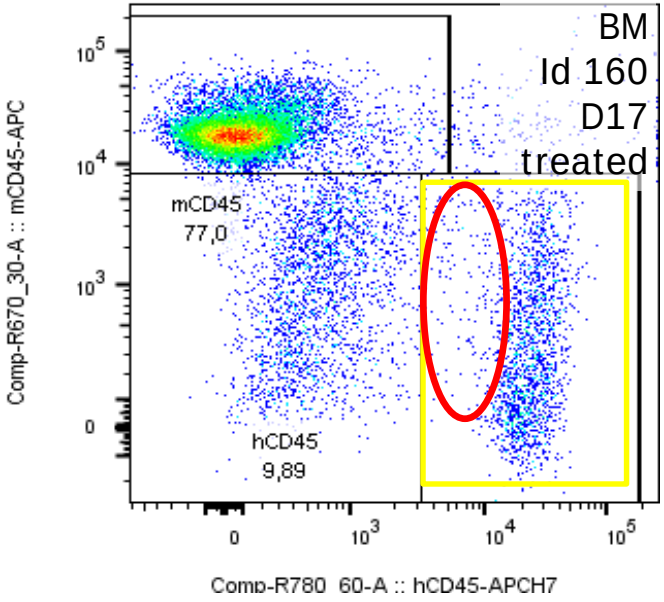


Humanized mouse platform: MOLM13 AML model









Available strain for human immune system reconstitution

MODEL	huNOG-EXL	Humanized NSG-SGM3 (or hu-CD34-SGM3)	Humanized MISTRG
STRAIN	hGM-CSF/hIL3-NOG	NSG™-SGM3	MISTRG
ALSO KNOWN AS	IL3/GM-Tg	NSGS	-
NOMENCLATURE	NOD.Cg-*Prkdc*^{scid} *Il2rg*^{tm1Sug} Tg(SV40/HTLV-IL3,CSF2)10-7Jic/JicTac	NOD.Cg-*Prkdc*^{scid} *Il2rg*^{tm1Wjl} Tg(CMV-IL3,CSF2,KITLG)1Eav/MloySzJ	C;129S4-*Rag2*$^{tm1.1Flv}$ *Csf1*$^{tm1(CSF1)Flv}$ *Csf2/Il3*$^{tm1.1(CSF2/IL3)Flv}$ *Thpo*$^{tm1.1(TPO)Flv}$ *Il2rg*$^{tm1.1Flv}$ Tg(SIRPA)1Flv/J
BACKGROUND	NOG (NOD strain background)	NSG™ (NOD strain background)	Mixed BALB/c x 129S4
CYTOKINES EXPRESSED *(other modifications)*	Human GM-CSF (CSF2) Human IL-3	Human GM-CSF (CSF2) Human IL-3 Human KITLG (SF)	Human GM-CSF (CSF2) Human IL-3 Human M-CSF (CSF1) Human TPO *Human SIRPα*
CYTOKINE LEVELS	hGM-CSF ~35 pg/ml hIL-3 ~80 pg/ml[1]	hGM-CSF, hIL-3 and hKITLG ~2000-4000 pg/ml[2]	Not reported
PROMOTER	SV40	CMV	All under endogenous mouse promoters except GM-CSF under human promoter.
INCREASE IN MYELOID CELLS OVER BASE MODEL	~3 fold relative to NOG[1]	~1.5 to 5 fold relative to NSG[3,4]	~9 fold compared to Rag2/ Il2rg null and ~6 fold compared to NSG[5]
LIFESPAN UNENGRAFTED	Expected normal lifespan.	Expected normal lifespan.	Not reported.
LIFESPAN AFTER CD34+ HSC ENGRAFTMENT	Up to 7 months reported. High chimeric ratio mice develop anemia after engraftment.[3]	Up to 4 months in ongoing studies. Mice develop sporadic anemia after engraftment.[5]	3 weeks after engraftment reaches 10-20% chimerism in peripheral blood if pre-conditioned with irradiation (~10-12 weeks post-engraftment); lifespan may be prolonged by using less potent stem cells, lower cell numbers or avoiding pre-conditioning.[5]
OTHER COMMENTS	Stable engraftment through lifespan of mouse	Loss of human graft after 3-4 months[5]	

Tested with Macrophage activation syndrome (MAS) in hu-NSG-SGM3 confirmed

Wunderlich et al.
JCI Insight. 2016;1(15):e88181

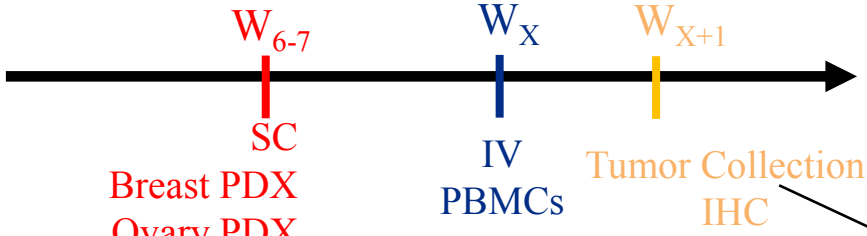
Evaluation of immune infiltrate in PDX tumors xenografted in humanized mice (1)

Question : best model for tumor immune infiltrate in mice reconstituted with human Immune cells - PBMC or CD34+ huSC as source of human cells?

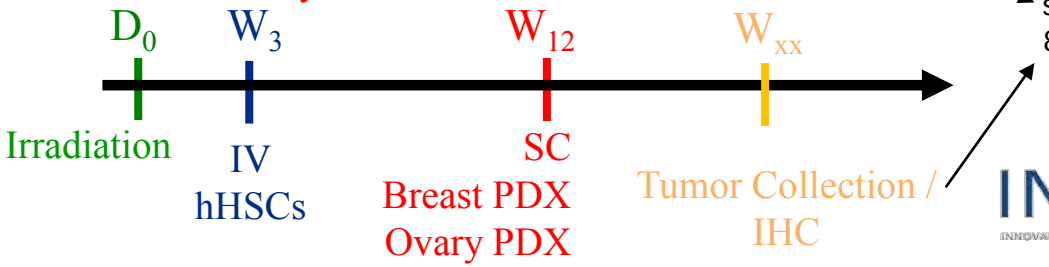
- *Design : 4 PDX - PBMC versus CD34+ huSC*

ID# PDX	patient infiltrate	NOG – PBMC	NOG-EXL-CD34+
OD-BRE-0589	+/-	3	3
IM-BRE-044	+++	3	3
IM-OVA-512	+/-	3	3
IM-OVA-535	+++	3	3

NOG + hPBMCs



NOG-EXL + hHSCs



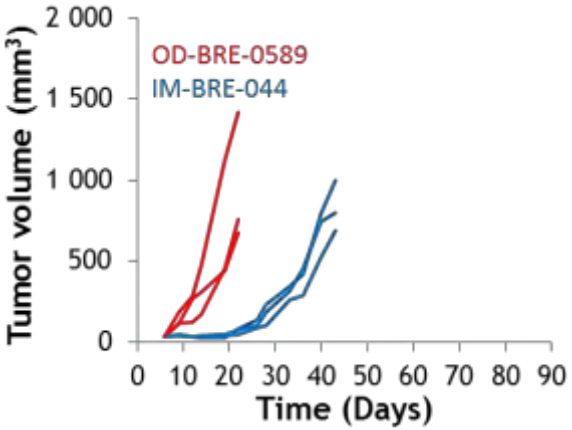
sacrifice at TV ~ 800-1,200 mm³

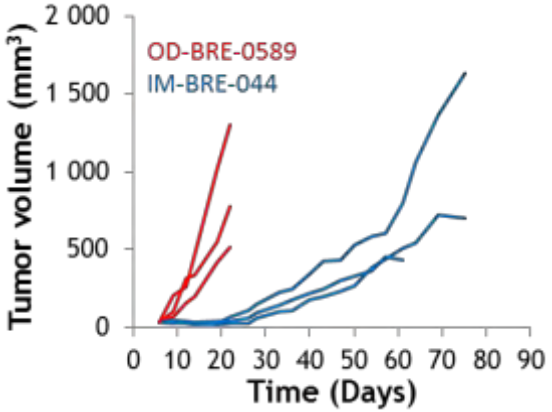
Evaluation of immune infiltrate in PDX tumors xenografted in humanized mice (2)

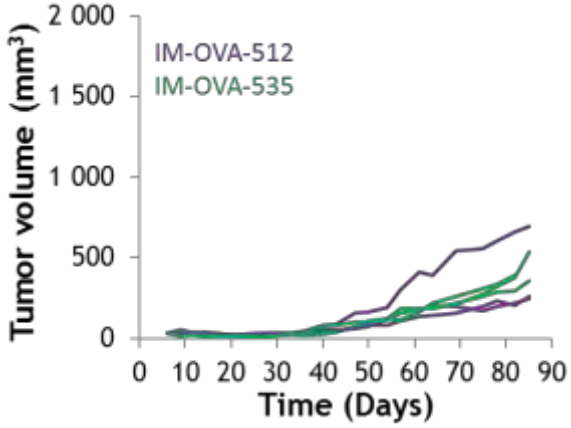
- Tumor growth

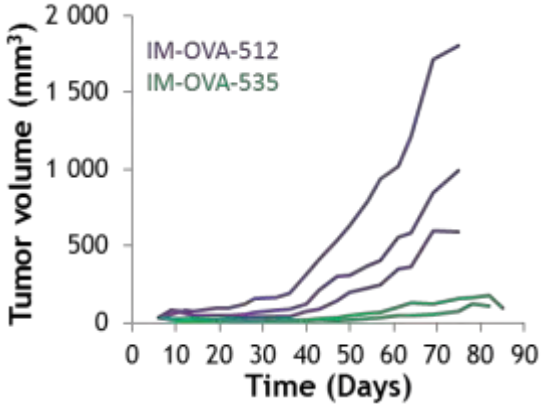
NOG + hPBMCs

NOG-EXL + hHSCs









Evaluation of immune infiltrate in PDX tumors xenografted in humanized mice (3)

Tumor	Mouse model	hCD45	hCD3	hCD8	hFoxP3	hPD-L1	CD163
OD-BRE-0589 (poorly infiltrate in patient)	NOG-PBMC	0	0	0	0	1	nd
		0	0	0	0	0	nd
		0	0	0	0	0	nd
	NOG-EXL (HSC)	1	0	0	0	0	nd
		0	0	0	0	0	nd
		1	0	0	0	0	nd
IM-BRE-044 (highly infiltrate in patient)	NOG-PBMC	1	1	1	1	2	0
		2	2	2	1	2	0
		1	1	1	0	2	0
	NOG-EXL (HSC)	3	3	3	3	2	2
		3	3	3	3	2	3
		3	3	3	3	1	3

scoring based on staining intensity for PD-L1 and density for other

- 0
- 1
- 2
- 3

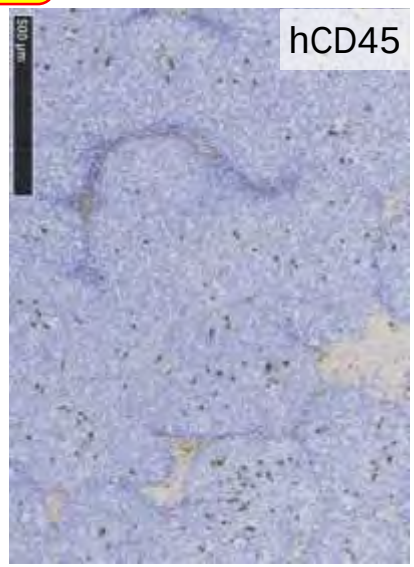
→ No difference in infiltration in both Ovary PDX models

Nd : not done

Evaluation of immune infiltrate in PDX tumors xenografted in humanized mice (4)

IM-BRE-044

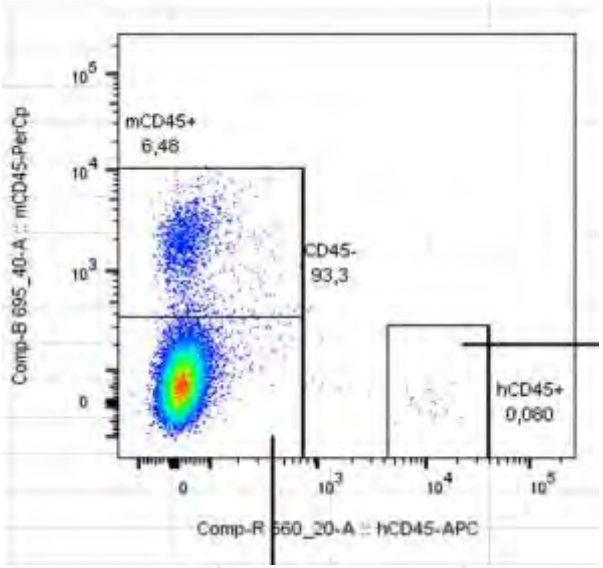
NOG-EXL + hHSCs



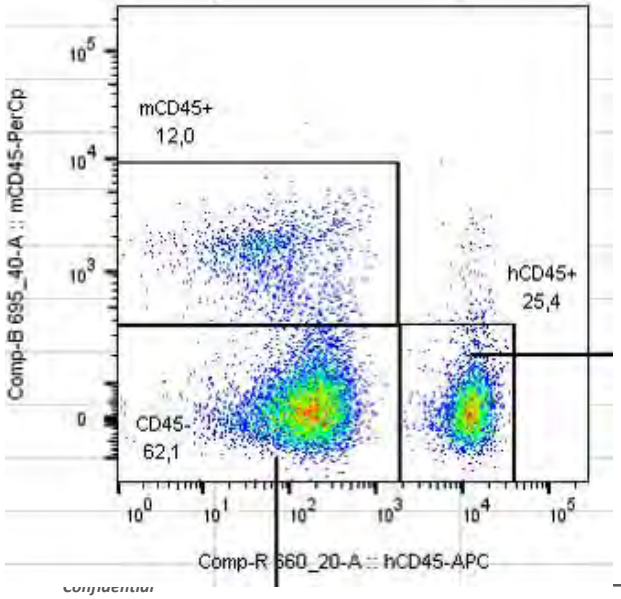
NOG + hPBMCs

Humanized mouse platform : Kinetics of tumor T cell infiltration

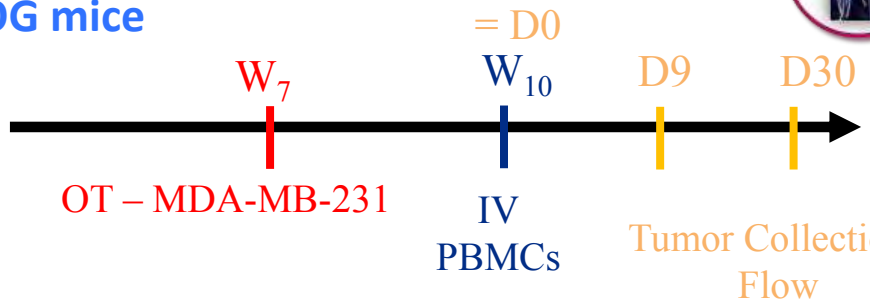
D9

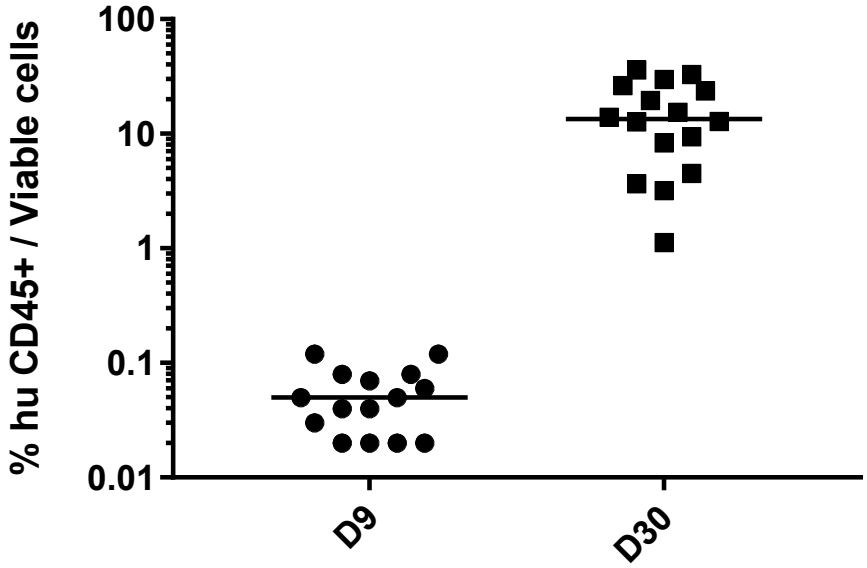


D30



NOG mice





	D9	D30
Mean :	0.055 %	15.9 %

Special Thanks to all the teams & their technicians

Olivier Duchamp

In vivo sciences (Les Ulis)
- Edwige Nicodeme

In vivo sciences (Dijon)
- Cyril Berthet
- Damien France
- Marc Hillairet De Boisferon
- Nicolas Hoffmann
- Sylvie Maubant
- Caroline Mignard
- Peggy Provent
- Olivier Raguin
- David Vallerand

In vivo sciences (Synergie MTL)
- Jill Rochetti

Jean-François Mirjolet

In vitro sciences (Les Ulis)
- Didier Grillot
- Akanksha Gangar

In vitro sciences (Dijon)
- Josselin Caradec
- Anne-Lucie Nugues
- Guillaume Serin

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