Thérapie cellulaire et tolérance immunologique

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Bécancour, 2019-10-12

SQT Société Québécoise de Transplantation

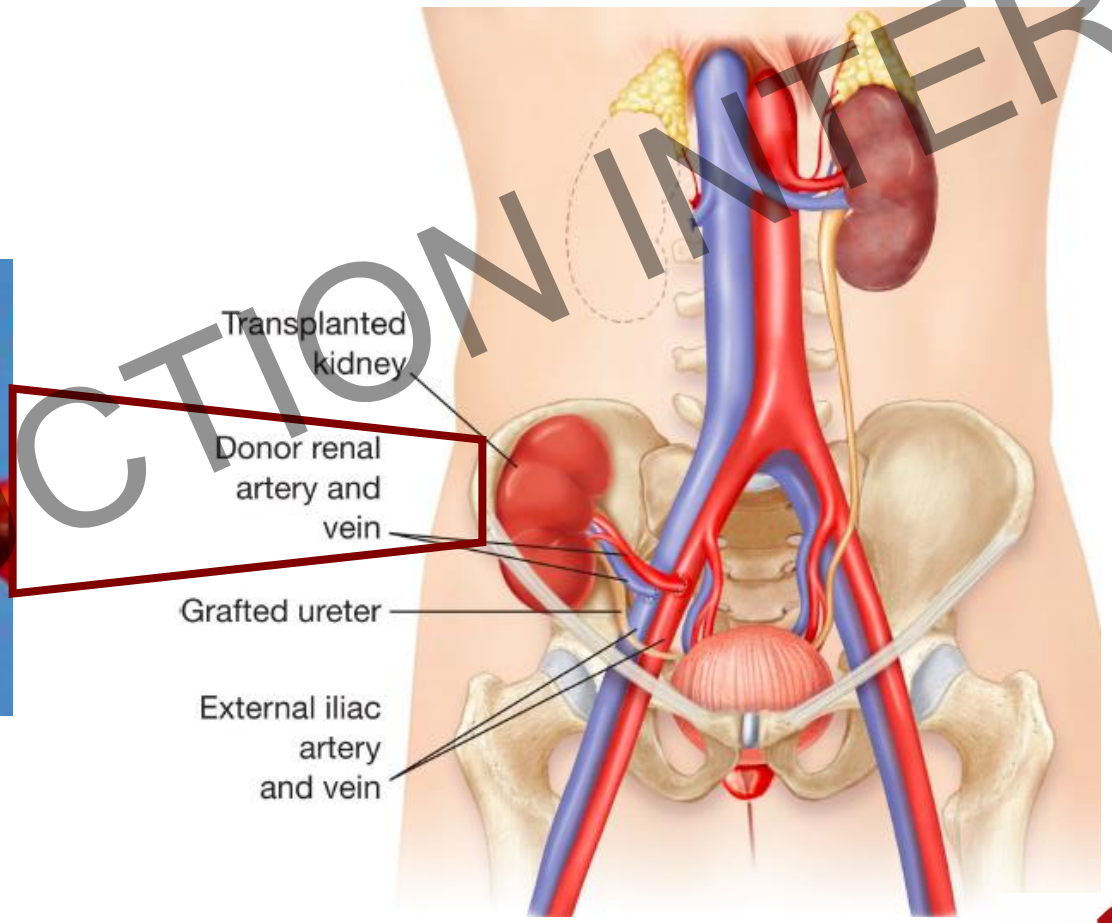
Conflit d’intérêt

- Kiadis Pharma: Brevet détenu par Université de Montréal et Hôpital Maisonneuve-Rosemont
- SpecificiT: subvention de recherche
- Novartis: consultant
- Jazz: consultant
- Pfizer: conférencier

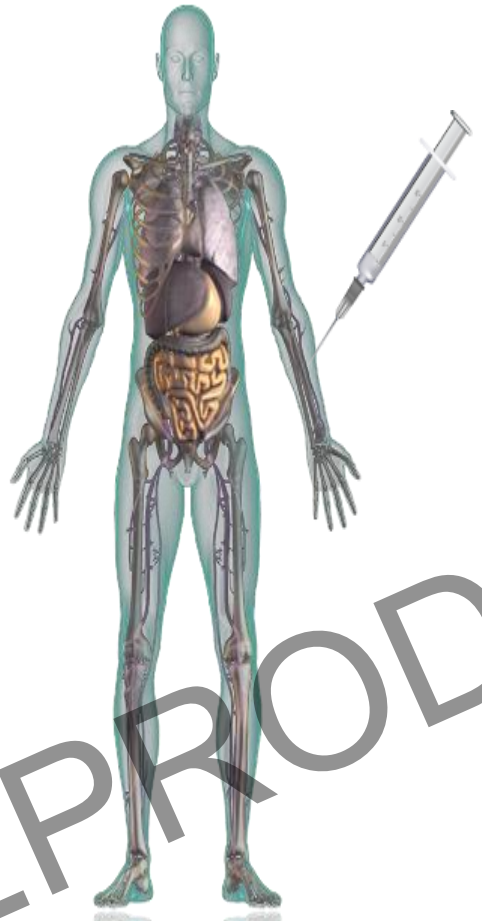
Rejet aigu

- Survient chez 12-15% des tous les greffés rénaux
- Peut causer une insuffisance rénale
- Peut amener la perte du greffon

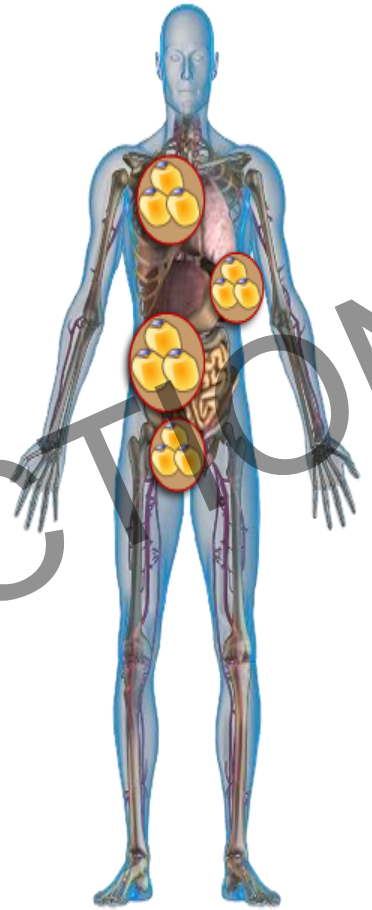
Rejet aigu



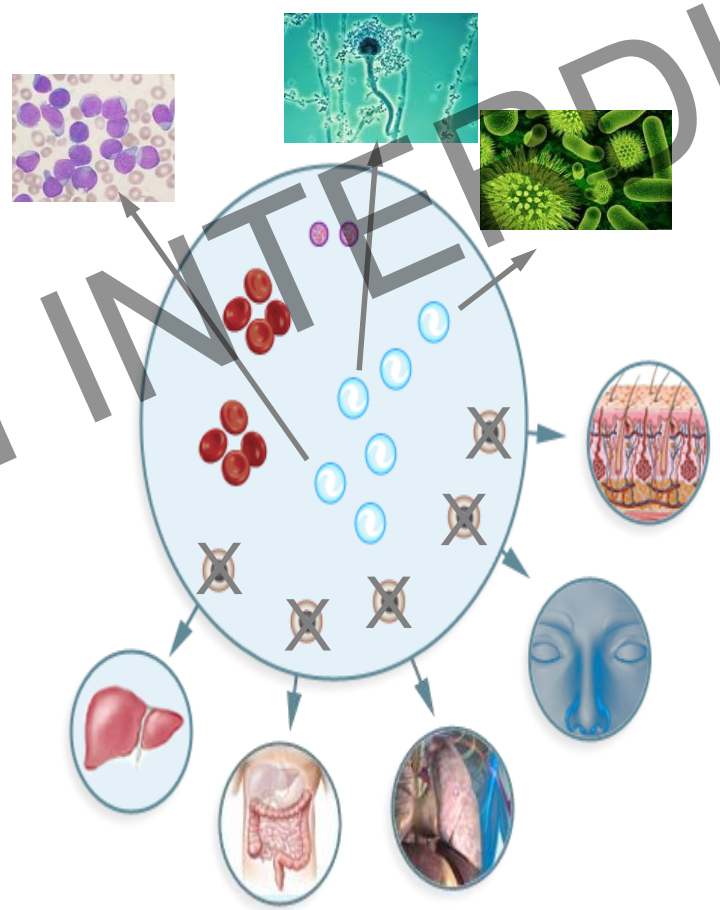
Greffes haplo-identiques



DONNEUR
HAPLO IDENTIQUE

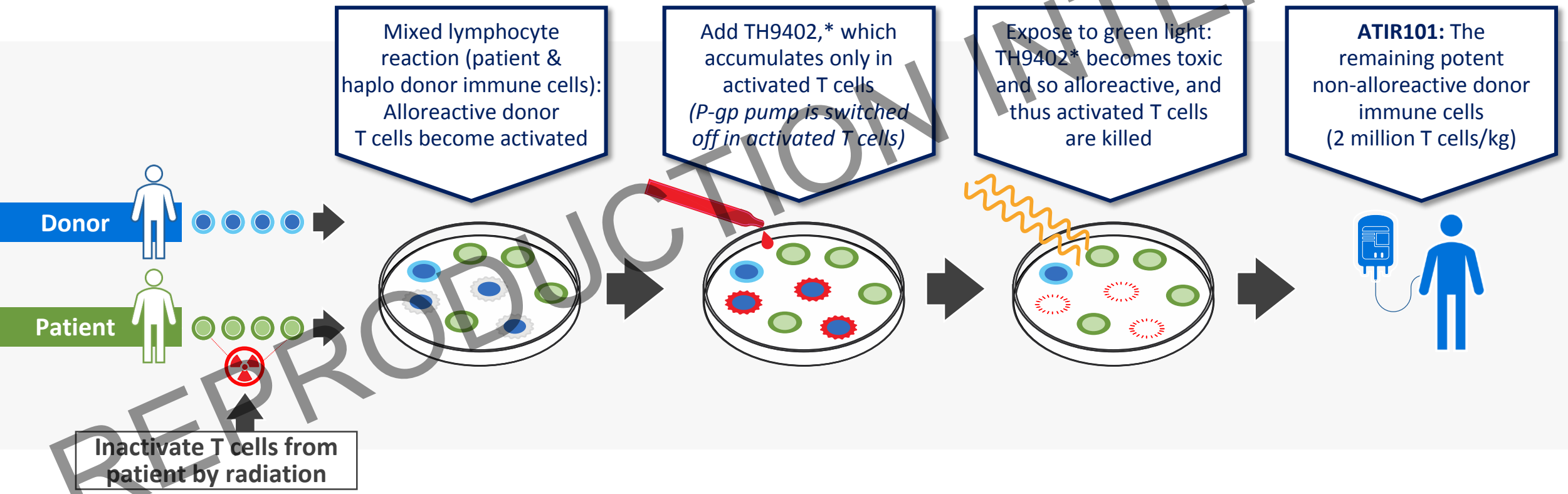


PATIENT LEUCÉMIQUE



ATIR101 Manufacture: Selective *Ex Vivo* Photodepletion of Alloreactive T Cells to Allow Adoptive Immuno-transfer After T-cell Depleted Haploidentical HSCT

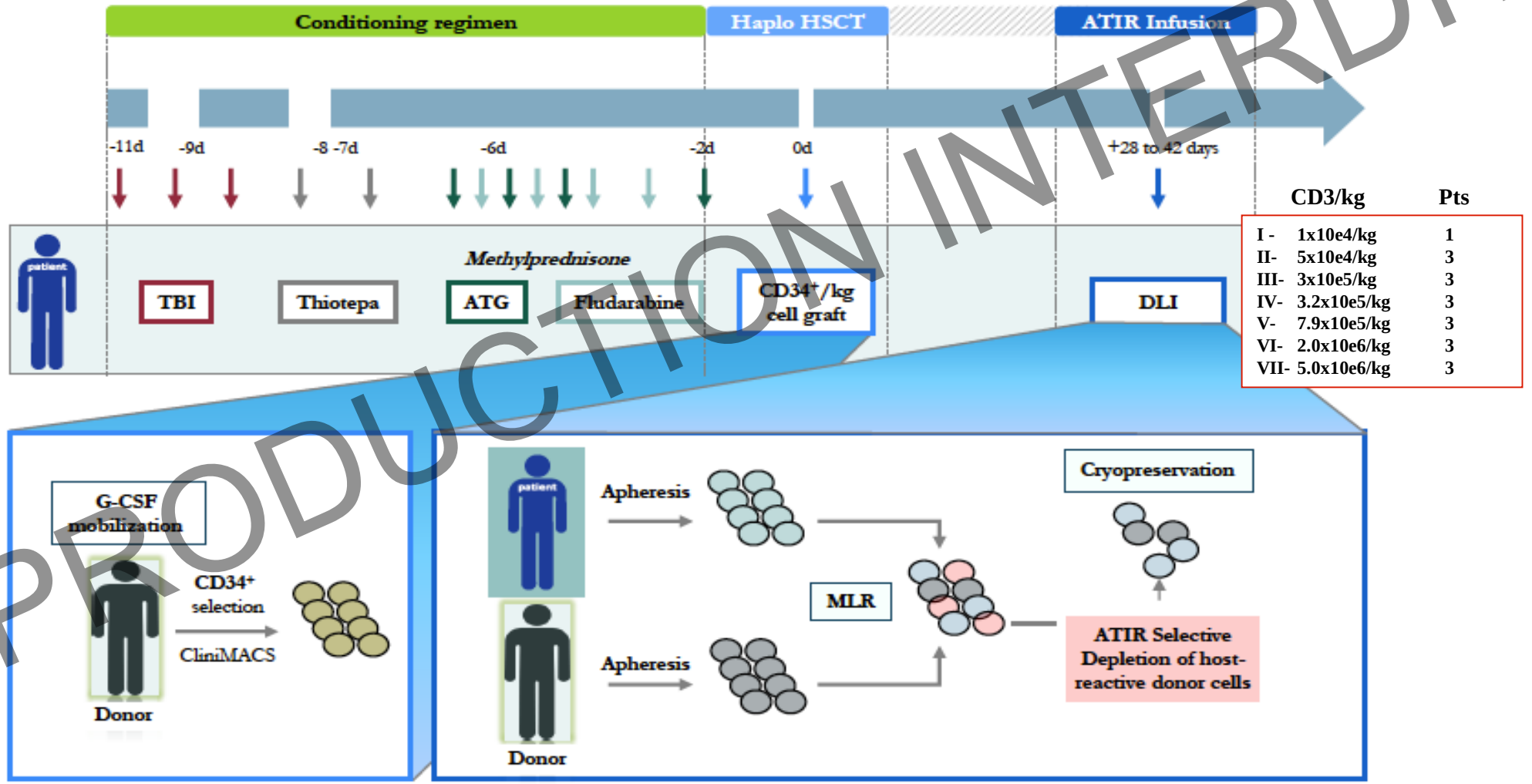
Rationale: Eliminate alloreactive T cells from DLI; preserve long-lasting immunity to fight infections and relapse; reduce the need for concomitant immunosuppressive therapy



* TH9402, selective rhodamine derivative.

Sélection de cellules souches

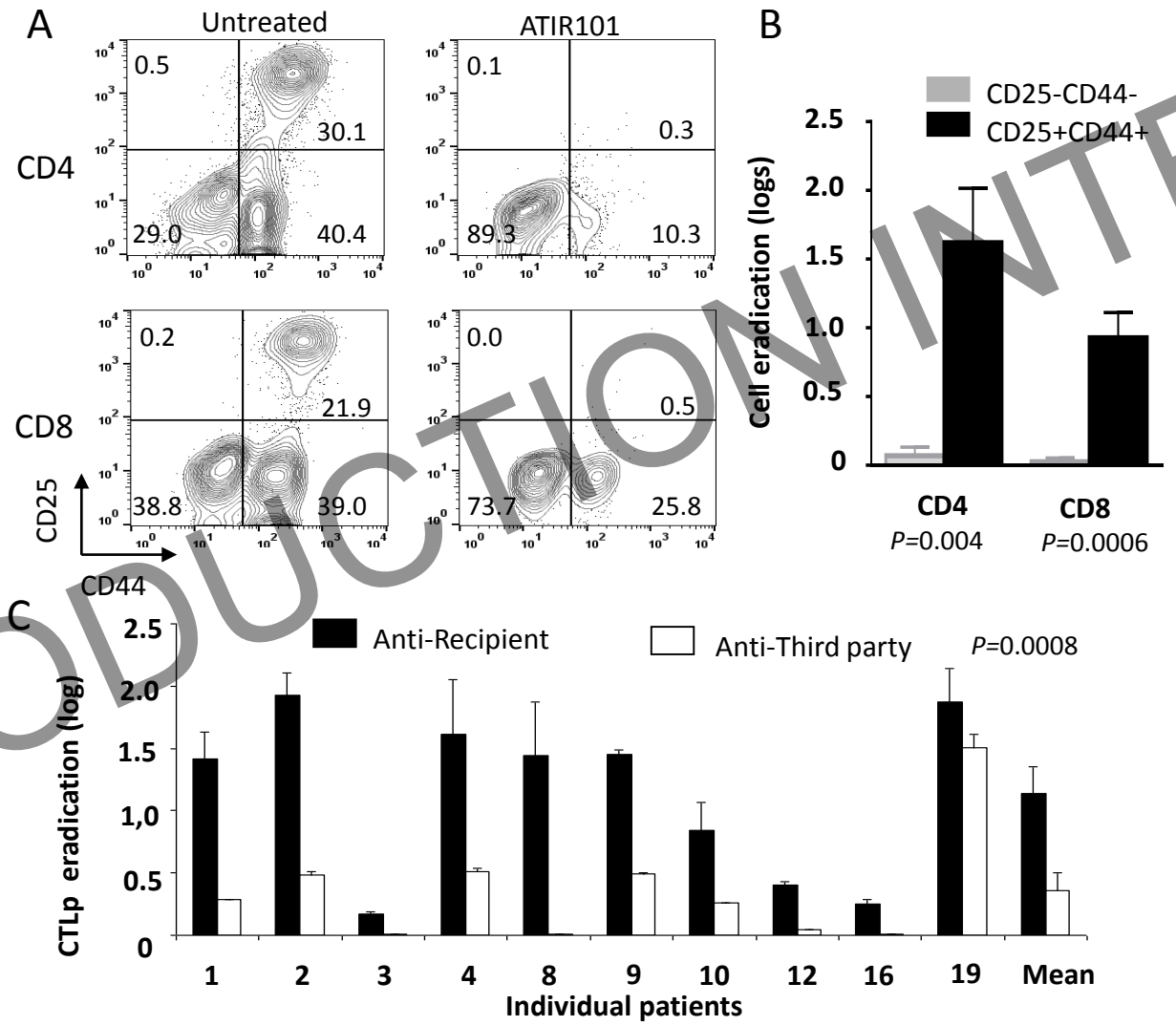
Haploidentical HSCT + ATIR: Phase I Clinical Trial at HMR high-risk hematologic malignancies



	CD3/kg	Pts
I -	1x10e4/kg	1
II-	5x10e4/kg	3
III-	3x10e5/kg	3
IV-	3.2x10e5/kg	3
V-	7.9x10e5/kg	3
VI-	2.0x10e6/kg	3
VII-	5.0x10e6/kg	3

DC Roy et al, Br J Haematol 2019

Photodepletion of activated / alloreactive T cells



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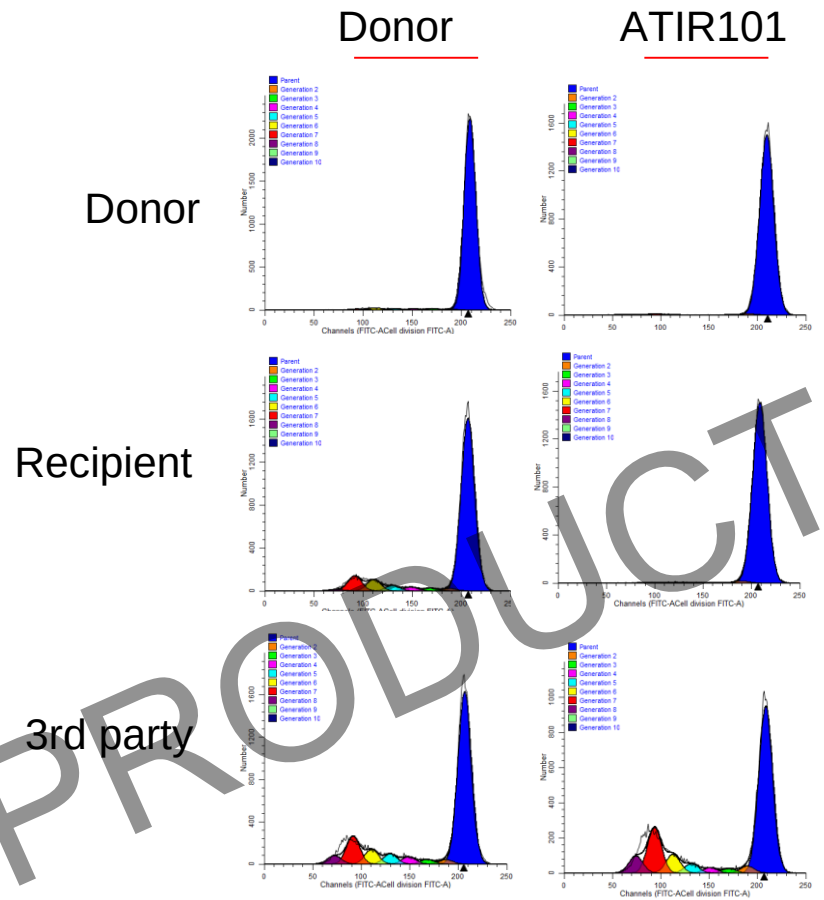
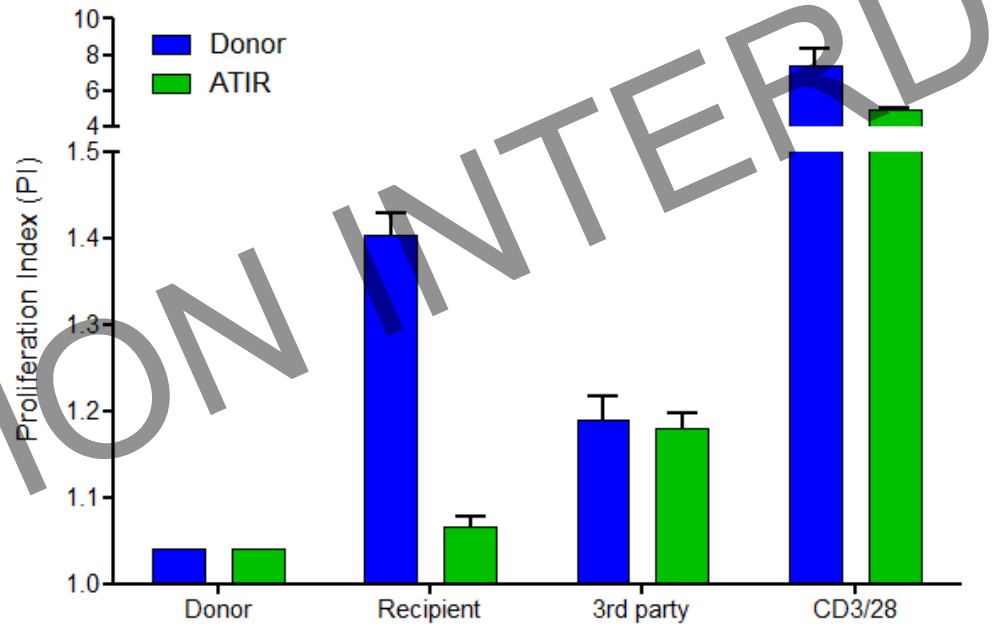
ATIR101: Proliferation assay





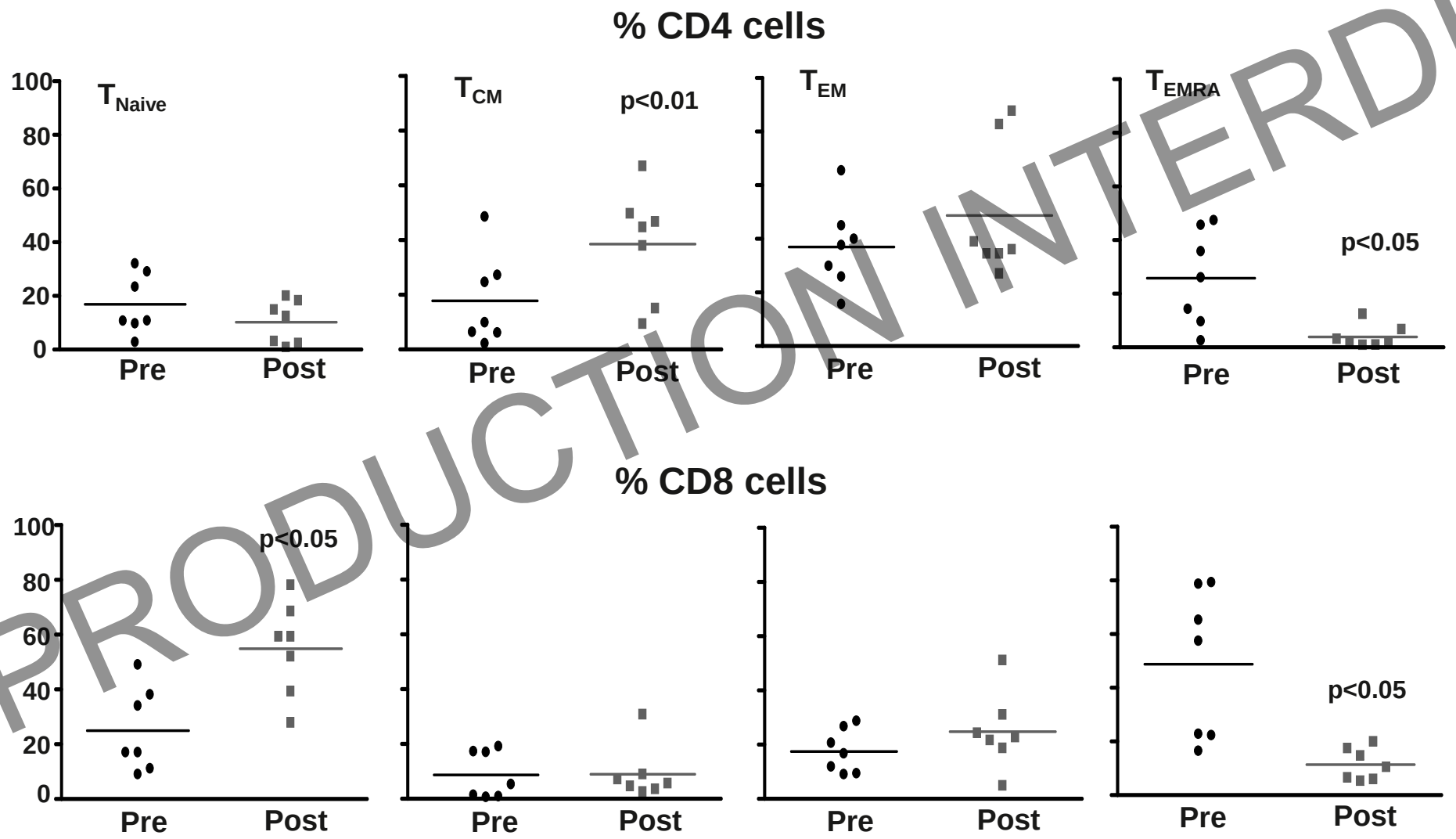
Avg. n=23 (Prol Index)	Donor	ATIR101
Baseline (autologous)	1.03	1.02
Recipient	1.32	1.04
3rd Party	1.56	1.44
Anti-CD3/28*	10.43	8.15

Engraftment and GVHD (CR-GVH-001)

	Median	Range
$CD34^+$ cells infused /kg	$10.5x10^6$	$6 - 15x10^6$
$CD3^+$ cells infused/kg	$1.4x10^4$	$0.4 - 2.6x10^4$
Neutrophils (>$0.5x10^9$/L)	10.0	8 - 20
Platelets (>$20x10^9$/L)	11.0	8 - 137

- ✓ Complete donor chimerism: all patients
- ✓ NO Graft rejection
- ✓ NO GVHD immunoprophylaxis
- ✓ **NO Grade III-IV GVHD**

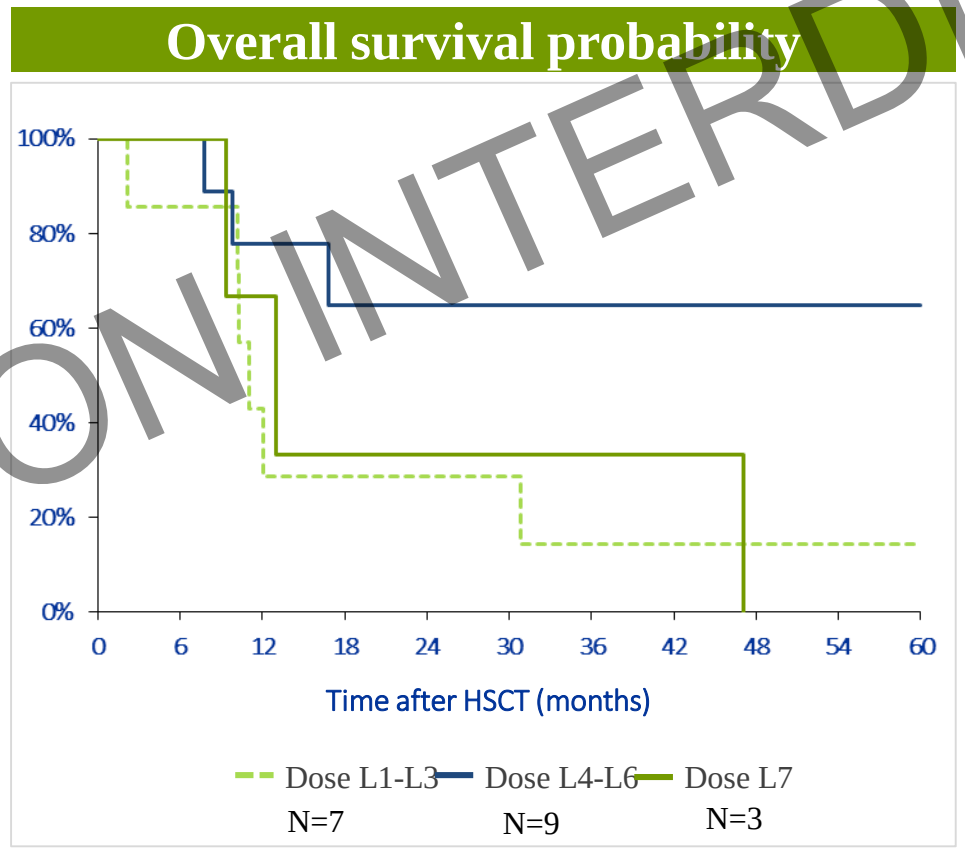
Impact of photodepletion on Memory T cell subsets



Patient outcome

	ATIR101 dose (cells/kg)	Survival	TRM	RRM
L1-L3	$1.0*10^4$	No	2 mo	
	$5.0*10^4$	No		10 mo
	$5.0*10^4$	No		31 mo
	$5.0*10^4$	No	11 mo	
	$1.3*10^5$	No	12 mo	
	$1.3*10^5$	No	10 mo	
	$1.3*10^5$	Yes		
L4-L6	$3.2*10^5$	Yes	NO TRM	
	$3.2*10^5$	Yes		
	$3.2*10^5$	Yes		
	$7.9*10^5$	No		8 mo
	$7.9*10^5$	No		10 mo
	$7.9*10^5$	Yes		
	$2.0*10^6$	No		17 mo
	$2.0*10^6$	Yes		
	$2.0*10^6$	Yes		
L7	$2.6*10^6$	No	47 mo	
	$5.0*10^6$	No	13 mo	
	$5.0*10^6$	No	9 mo	

RRM = relapse-related mortality
TRM = transplant-related mortality



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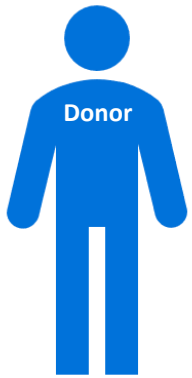
Procedure of CD34-selected Haploidentical HSCT With the Addition of ATIR101



Donor

T-cell depleted, CD34+ PBMC graft

Selective photodepletion to eliminate GVHD-causing T cells

Conditioning

- TBI (1200 cGy) or melphalan (120 mg/m^2)
- Thiotepa (10 mg/kg)
- Fludarabine (30 mg/m^2 x 5d)
- ATG (thymoglobulin: 2.5 mg/kg x 4d)

Haploidentical HSCT

- CliniMACS® CD34 isolation system (Miltenyi Biotec)
- Maximum of 3x10^4 CD3+ cells/kg

Engraftment

- Neutrophils (>0.5x10^9/L for 2 consecutive days)
- Platelets (>20x10^9/L for 3 consecutive days)

ATIR101 infusion

- Donor lymphocyte infusion
- 2x10^6 viable T cells/kg
- 28–32 days post-HSCT
- **No immunosuppression**

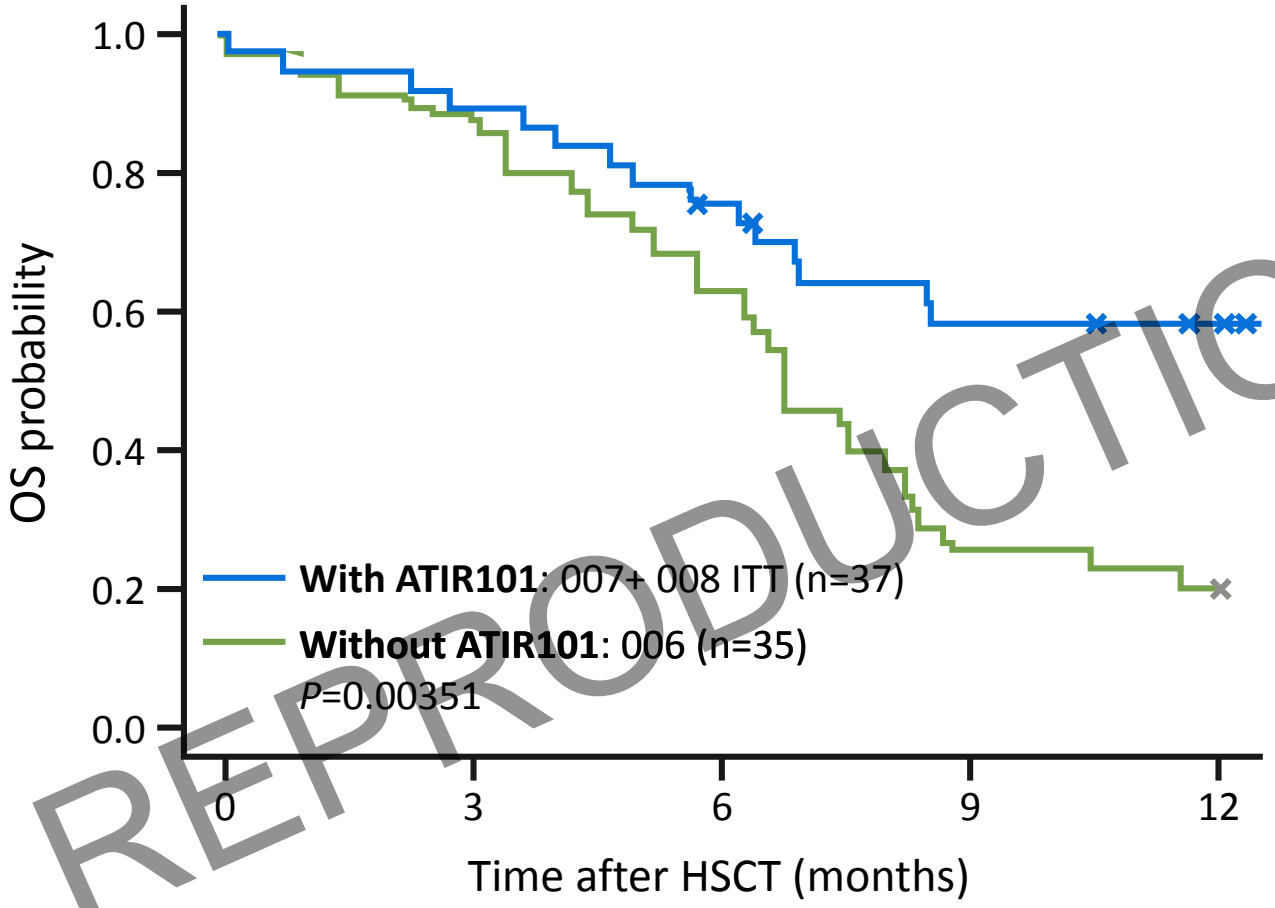
Patient Characteristics (N=37): ITT

Characteristics		CR-AIR-007 + CR-AIR-008 (N=37)
Median age, years (range)		46 (20–64)
Diagnosis, n	AML	24
	ALL	10
	MDS	3
Disease risk index,*n	Intermediate	21
	High	16
Preparative regimen, n	TBI	17
	Non-TBI	20
Median cell dose infused, range	$CD34x10^6$ cells/kg, median	10.5 (3.2–24.4)
	$CD3x10^4$ cells/kg, median	0.32 (0.00–1.80)
Engraftment, days	Platelets, median (range)	12 (7–35)
	Neutrophils, median (range)	14 (8–34)
ATIR101 infusion,† median days post-HSCT (range)		28 (28–73)

* Armand P et al. Blood 2014, 123: 3664-3371

† Five patients did not receive ATIR101.

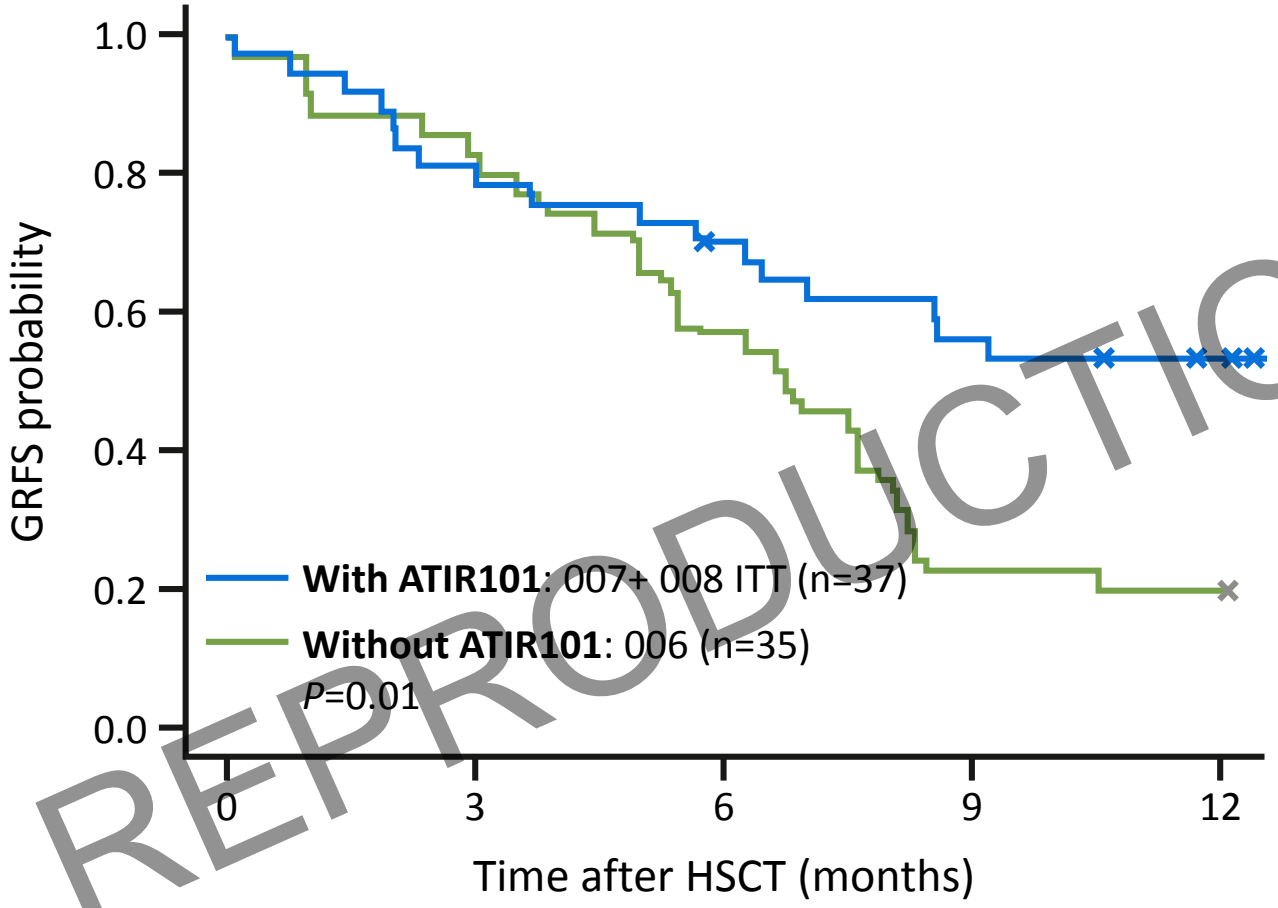
OS in Patients Receiving CD34-selected Haploidentical HSCT With or Without ATIR101



1-year post HSCT OS* (95% CI)	
With ATIR101	Without ATIR101
CR-AIR-007 + CR-AIR-008 (N=37)	CR-AIR-006 (N=35)
58% (44–77)	20% (10–39)

* Kaplan–Meier estimates (ITT population).

GVHD-free Relapse-free Survival (GRFS) in Patients Receiving CD34-selected Haploidentical HSCT With or Without ATIR101

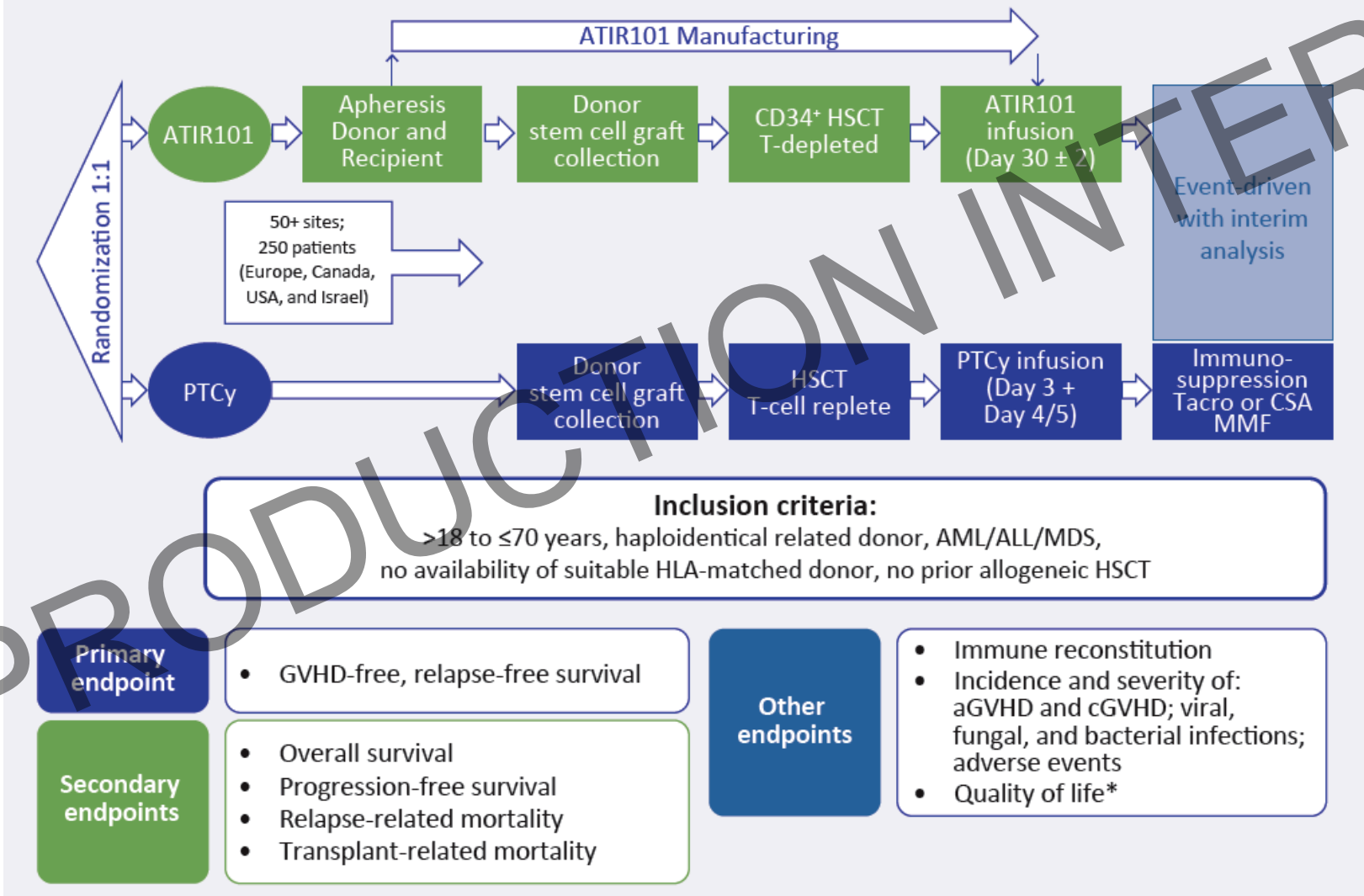


1-year post HSCT GRFS* (95% CI)	
With ATIR101	Without ATIR101
CR-AIR-007 + CR-AIR-008 (N=37)	CR-AIR-006 (N=35)
53% (39–72)	20% (10–39)

Greater GRFS estimates suggest clinical benefit of ATIR101 vs no ATIR101

* Kaplan–Meier estimates (ITT population). GVHD free/relapse-free survival (GRFS) is survival without acute GVHD (grade III/IV), chronic GVHD (requiring systemic treatment), and/or cancer relapse.

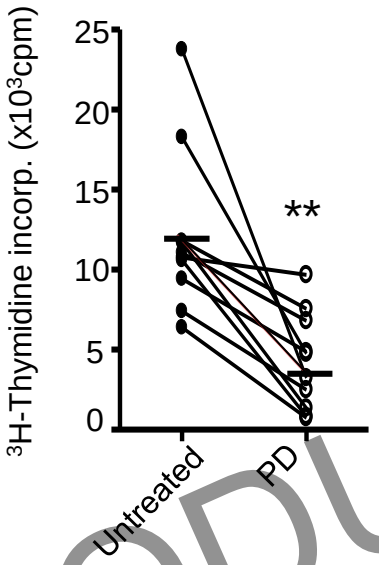
Phase III, HATCY study Comparing the Safety and Efficacy of Haploidentical T-Cell-Depleted HSCT with ATIR101 vs. Haploidentical T-Cell-Replete HSCT with PTCy in Patients with Hematologic Malignancies

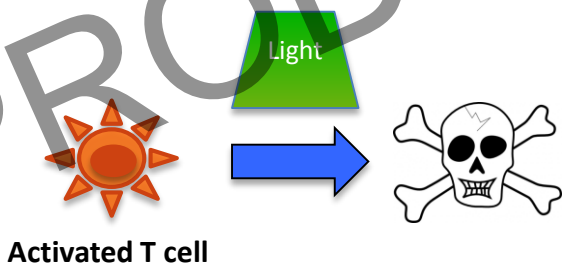


*FACT-BMT, SF-36, MDASI and EQ-5D-5L total scores. CSA, cyclosporin; MMF, mycophenolate mofetil.

ECP-001 Trial: Biological Observations

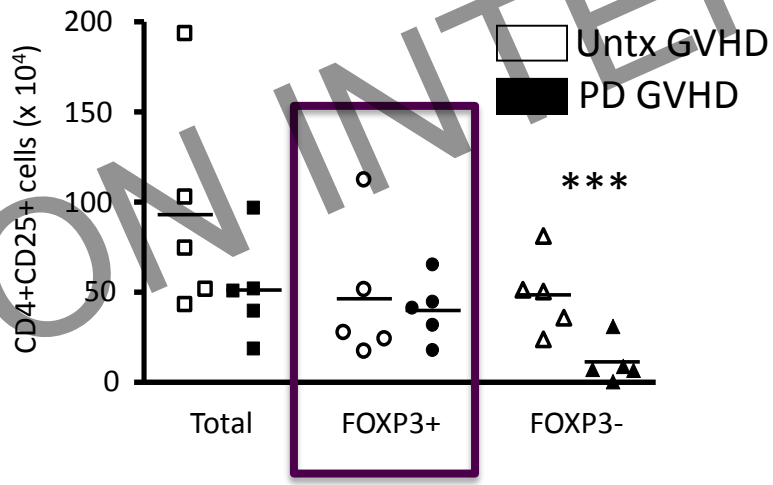
Decrease of proliferating cells

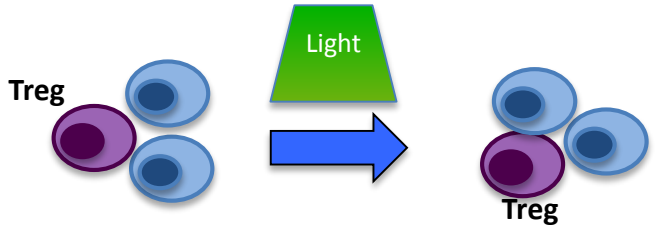




PBMCs from chronic GVHD patients (n 10) were exposed (or not) to photodepletion. Proliferation of GVHD cells was assessed by 3H-thymidine incorporation after 5-day cultures in the presence of IL-2.

Preservation of FOXP3+ Tregs

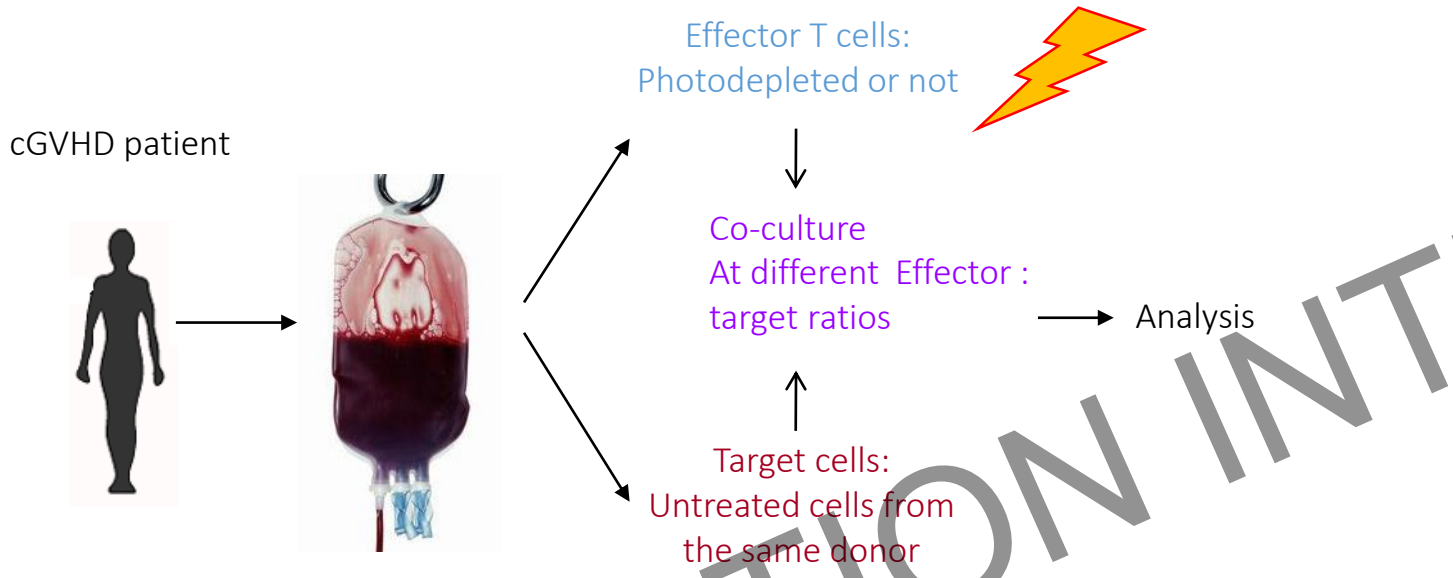


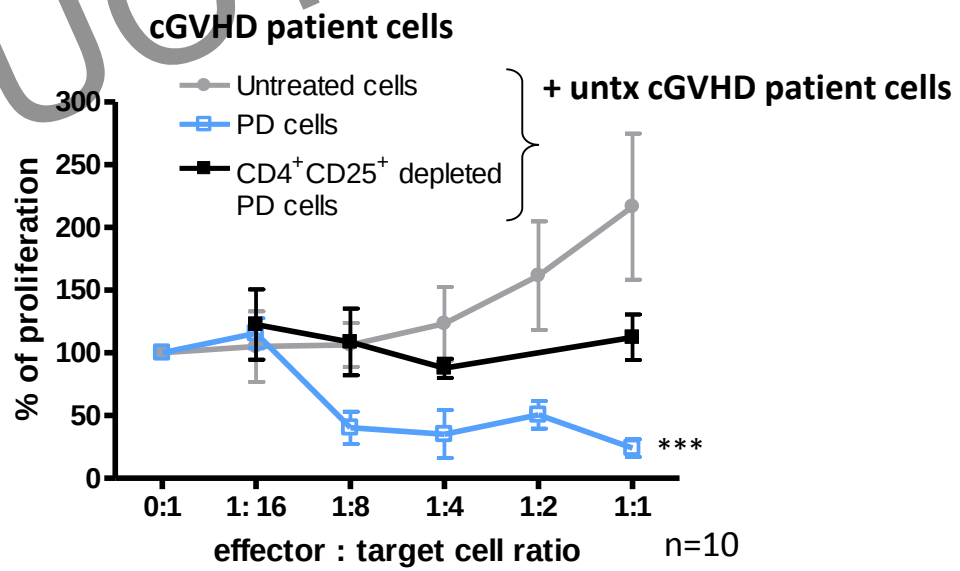


Shown are representative examples and a compilation of 6 independent experiments.+/- SD expressed in absolute number. Clear bars and filled bars represent untreated (untx) and photodepletion-treated GVHD PBMCs, espectively. **P .01 and ***P .001

Bastien et al, Blood, 2010

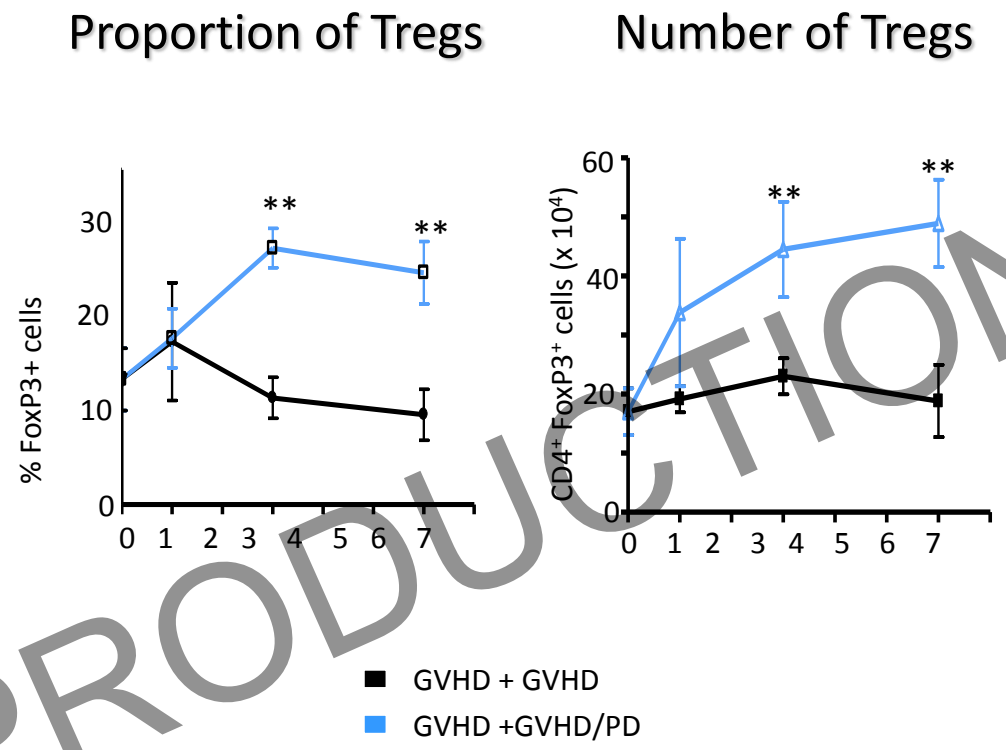
TH9402 photodepletion (PD) preserves functional Tregs present in cGVHD patients

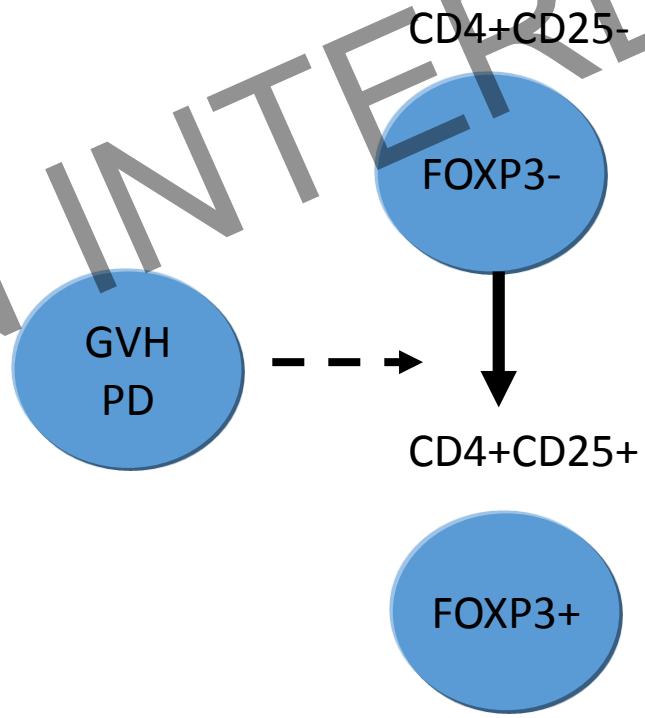




Bastien et al, Blood, 2010

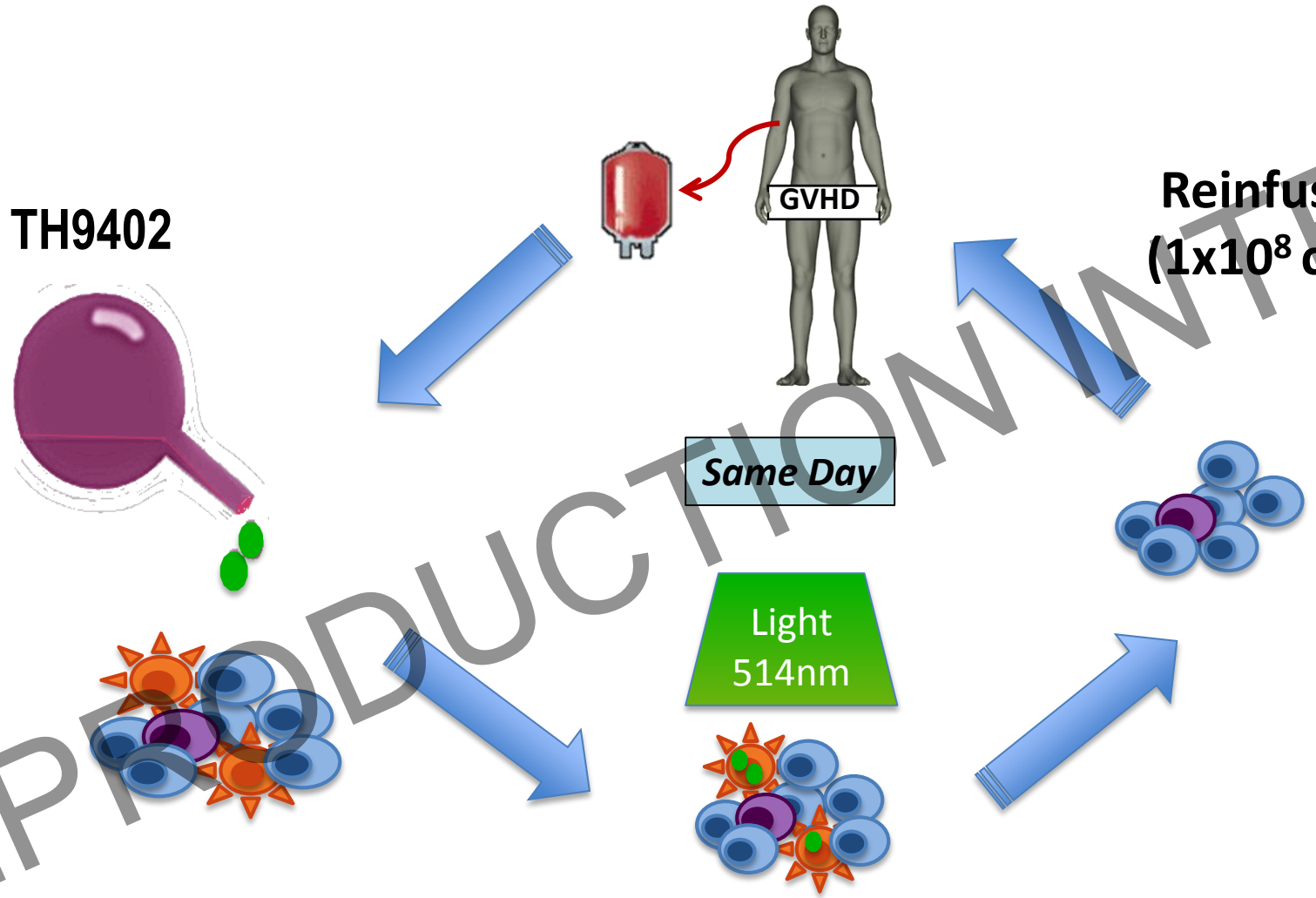
PD treated cells lead to an increase in the number of Tregs





Bastien et al, Blood, 2010

ECP-001 Trial: TH9402 PDT treatment of GVHD Patients

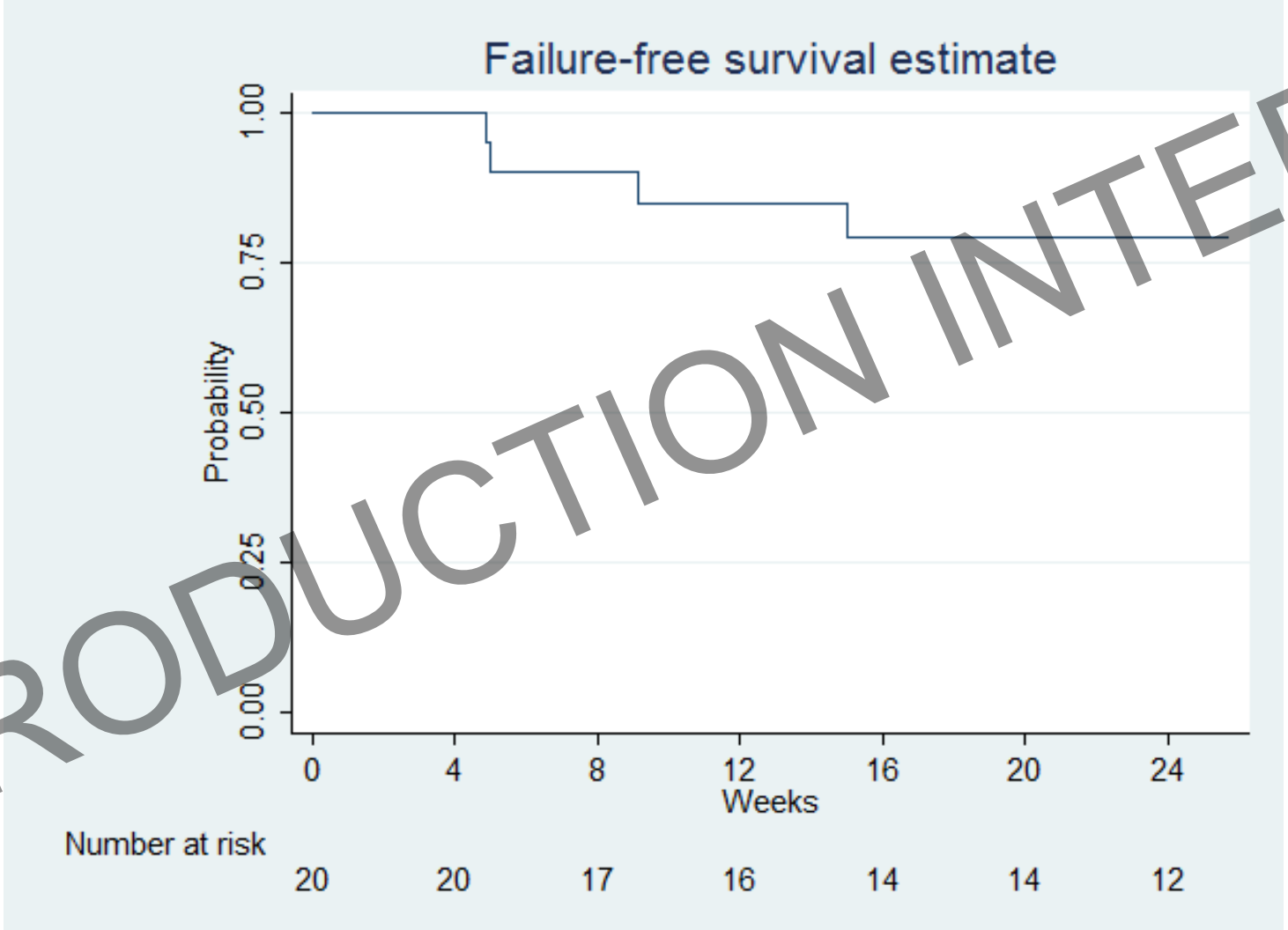


15 traitements en 24 semaines

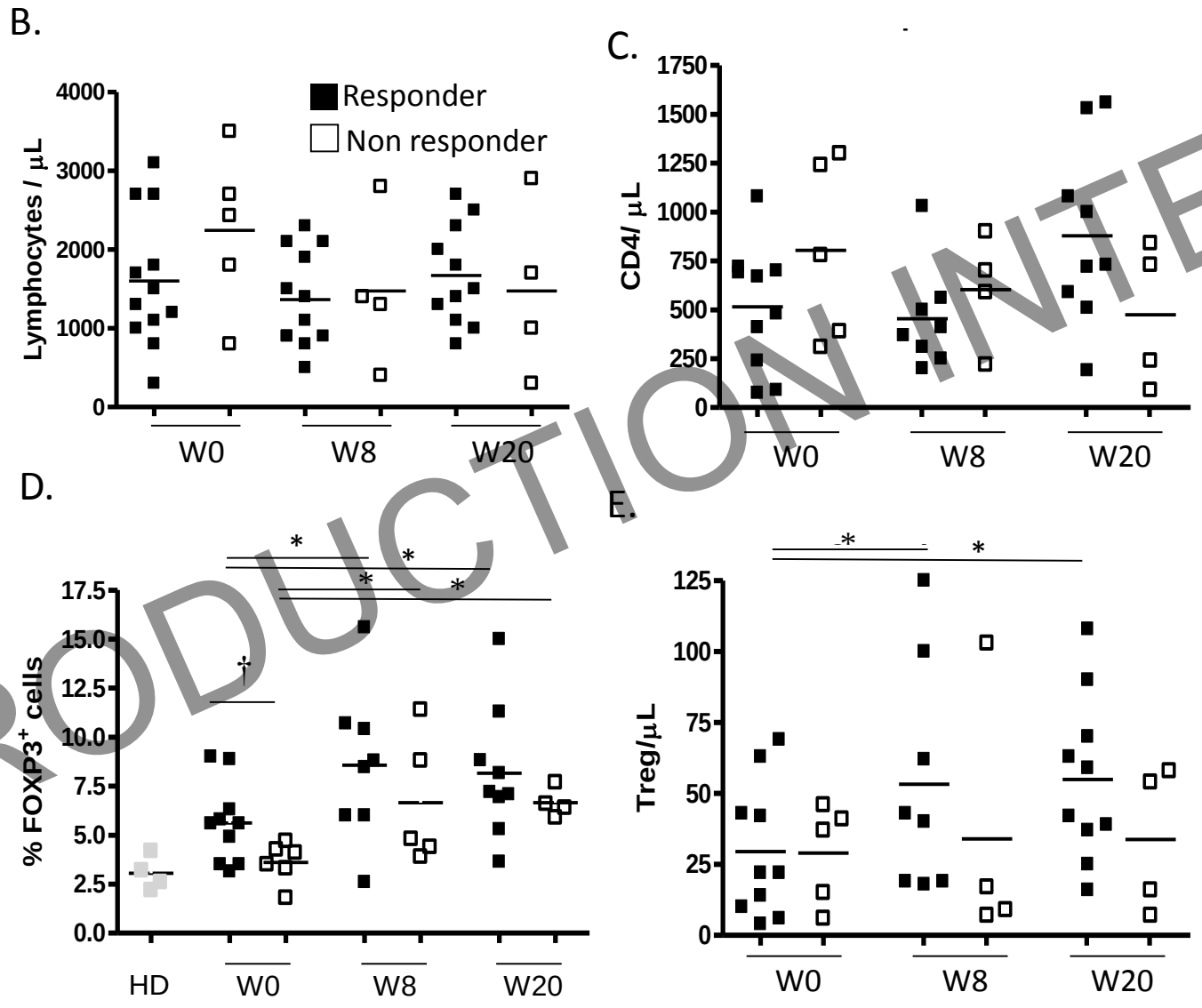
ECP-001 Trial: TH9402 PDT treatment of GVHD Patients

- Response in at least one organ in study subgroups	
Total	11/18 (61)
Concentration of photosensitizer	
PDT 0.33 µM	4/10 (40)
PDT 1.32 µM	4/8 (50)
Type of onset of cGVHD	
De novo	4/5 (80)
Progressive	2/7 (29)
Quiescent	2/6 (33)
Akpek risk group	
Low	5/8 (63)

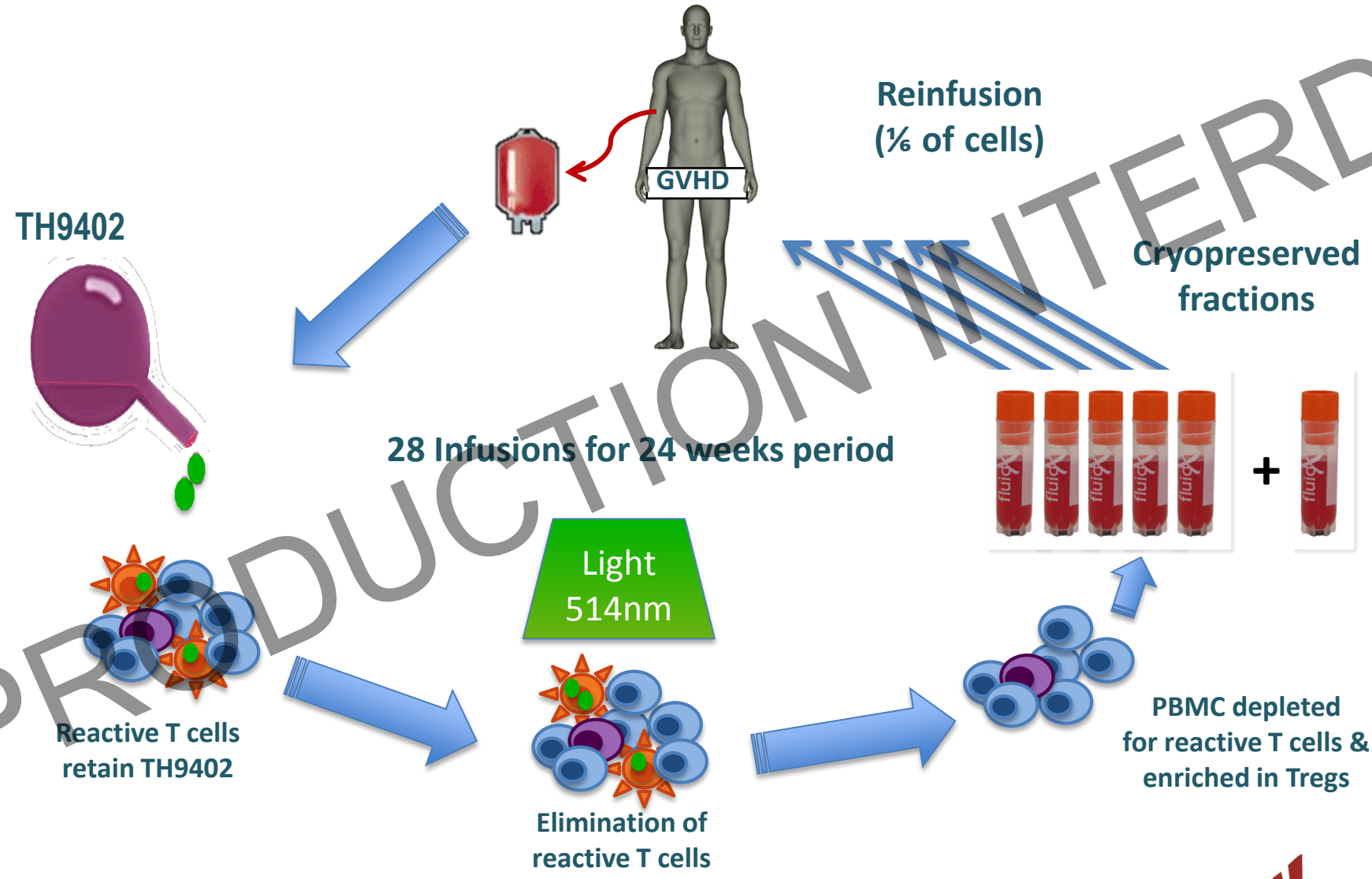
ECP-001 Trial: TH9402 PDT treatment of GVHD Patients



Etude clinique ECP-001: Augmentation des Trégulateurs



CARE-001: Phérèses intermittentes pour traitement de GVH



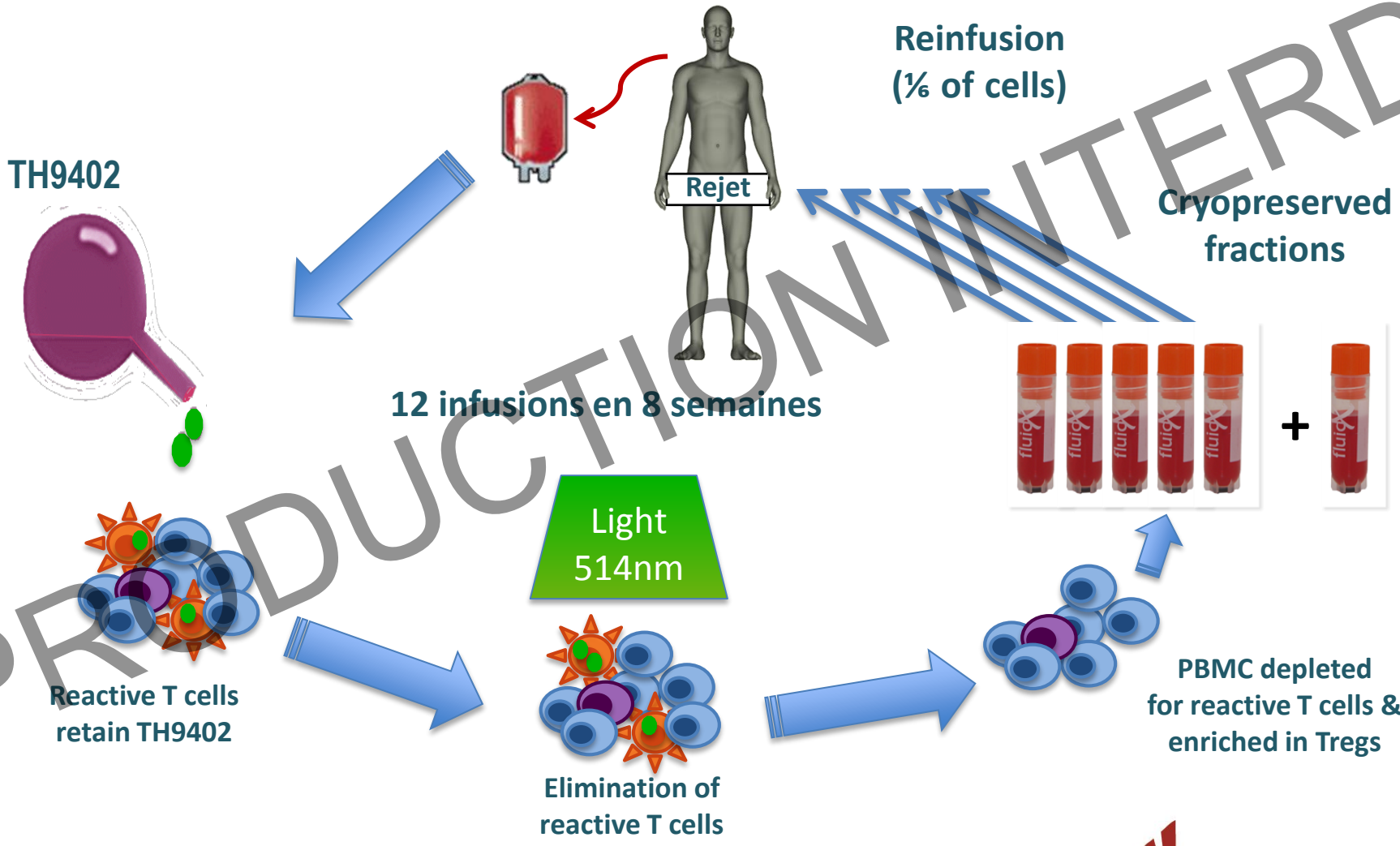
CDTRP

Approche CARE vs ECP-001

Innovations avec CARE	CARE	ECP-001
➢ Plus d'infusions	28 Infusions	15 Infusions
➢ Moins d'aphereses	6 Aphereses	15 Aphereses
➢ Cellules congelées	Frozen Cells	Fresh Cells
➢ Dose cellulaire	As per leukapheresis	Fixed 1×10^8

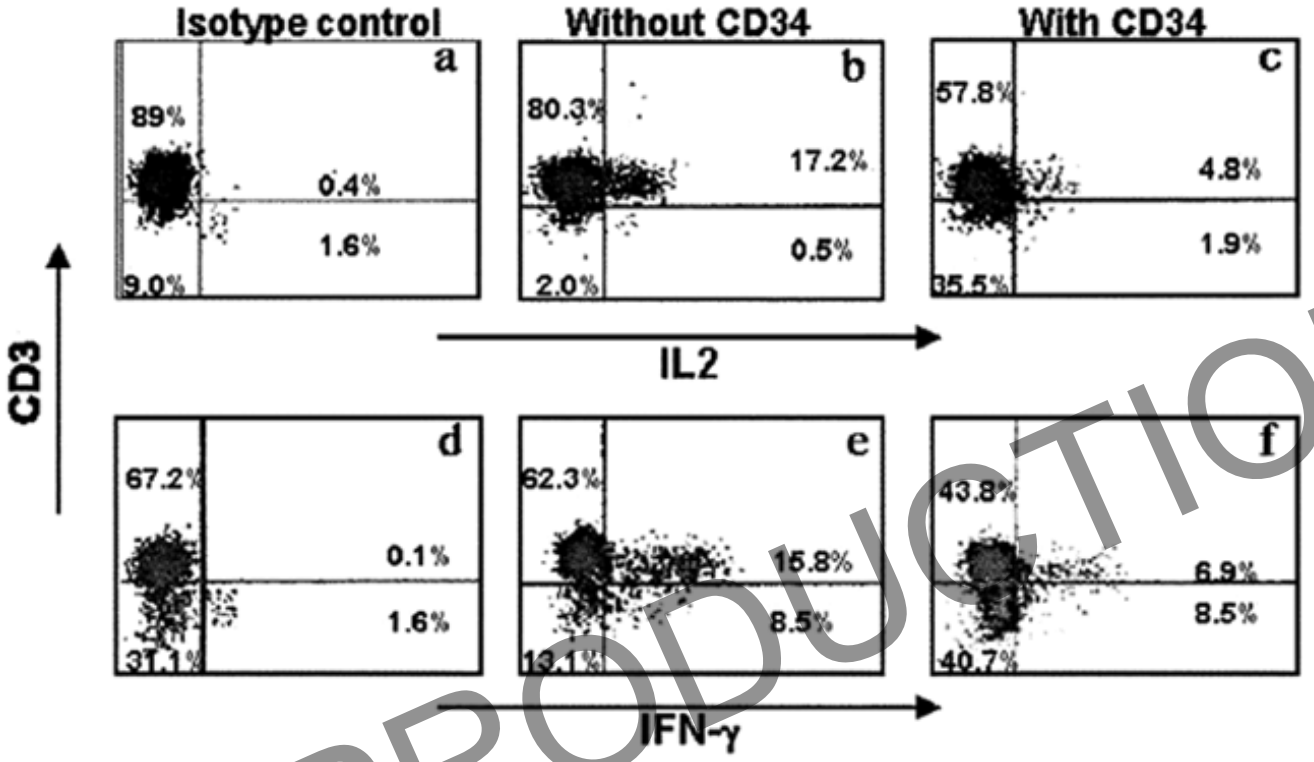
CARE-002: Traitement du Rejet de greffe rénale

(L Sénécal, S Colette, H Cardinal)

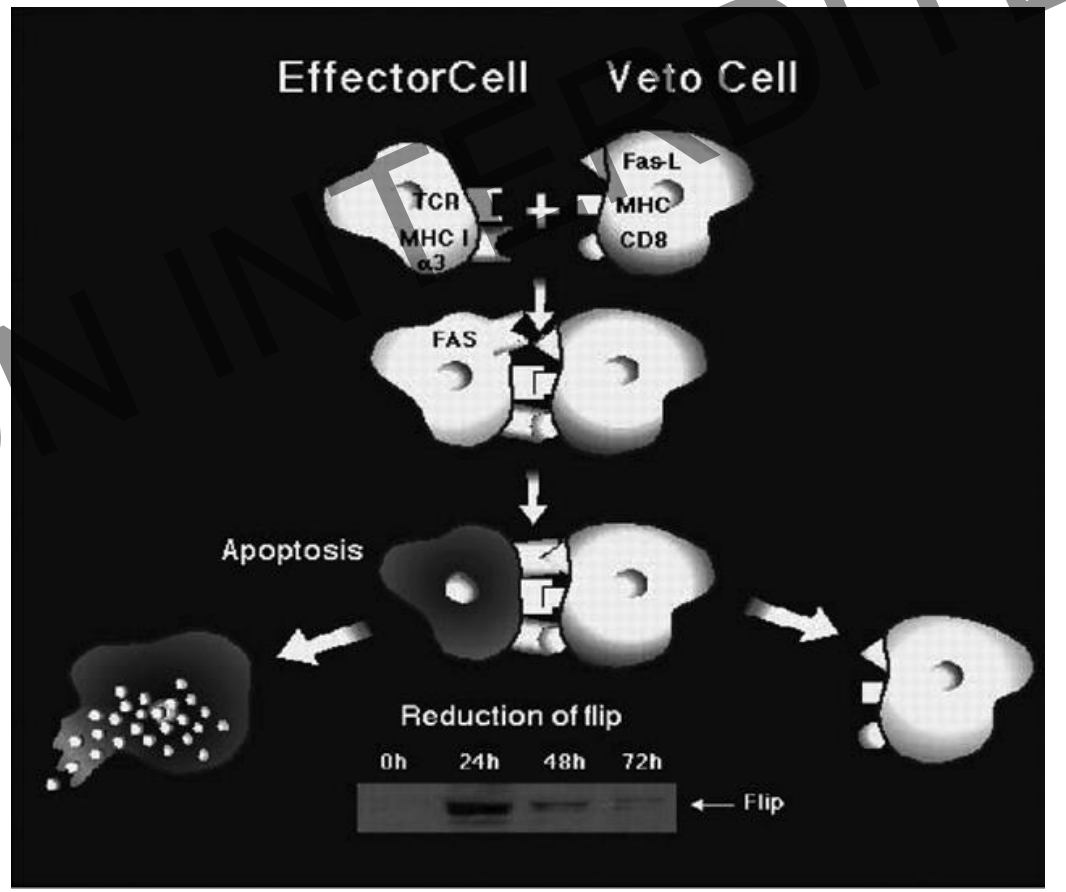


CDTRP et FRQS

Cellules souches CD34+ comme cellules Veto



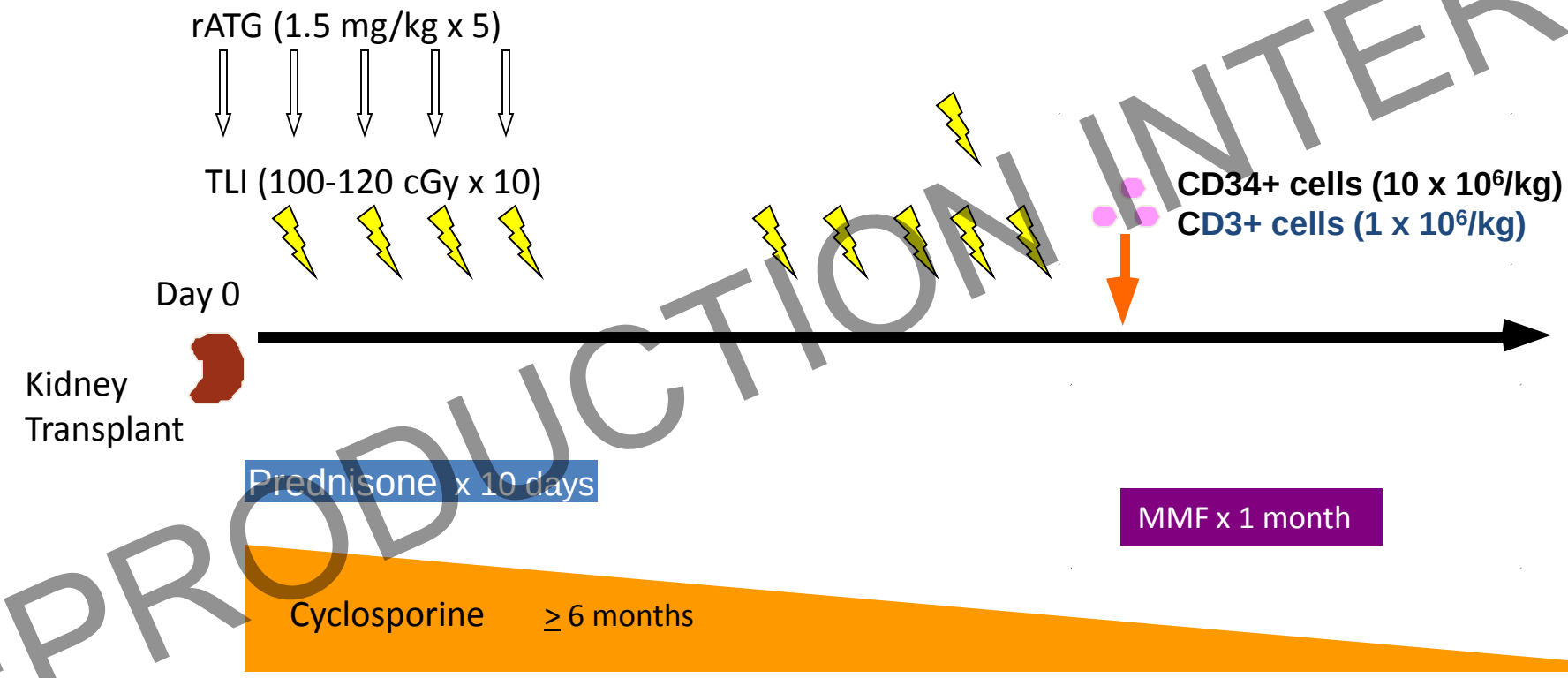
+CD8 Tcm



Reisner Y et al Ann NY Acad Sci 2009

Stanford Protocol : HLA-Matched

HLA-Matched Kidney and Hematopoietic Cell Transplantation Recipients' Procedures



Withdraw immunosuppression if:
-stable mixed chimerism >180 days
-no evidence of rejection
-no GVHD

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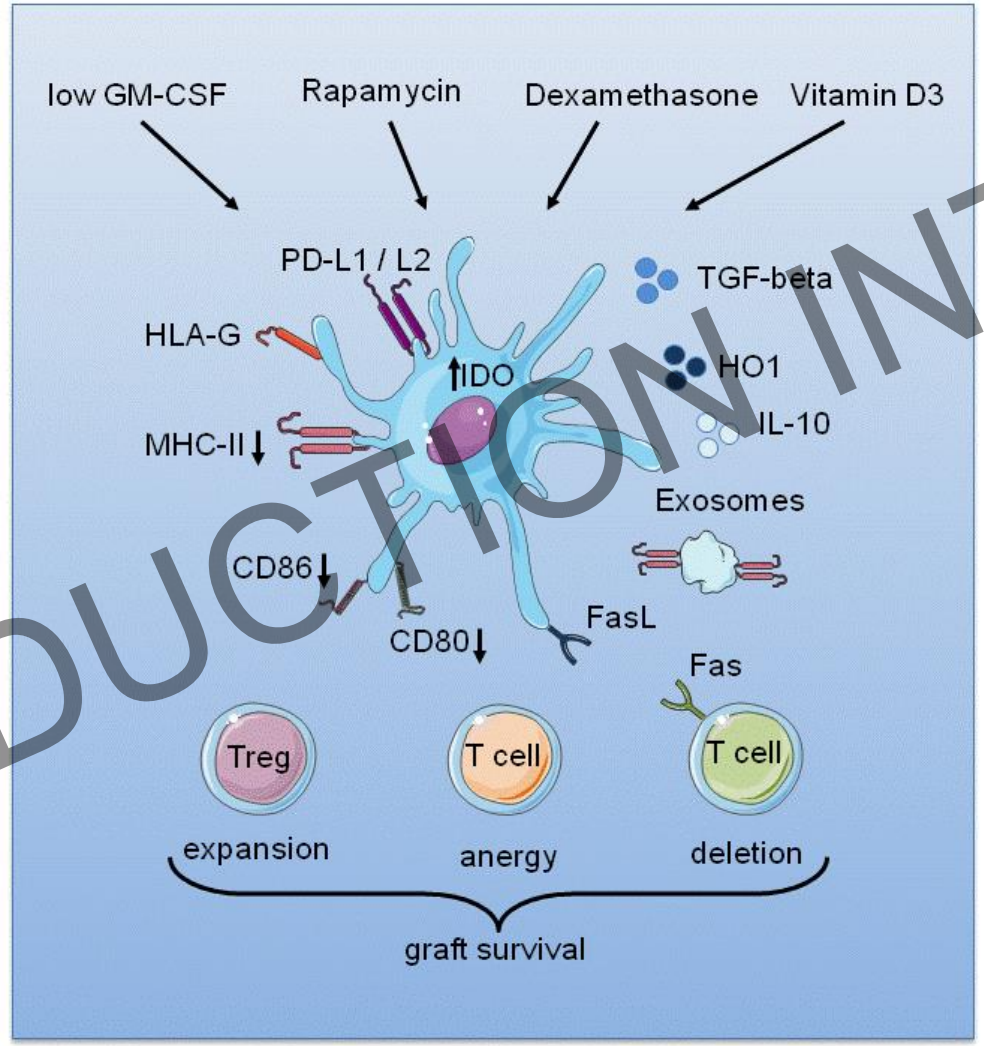
Cellules dendritiques induisant tolérance

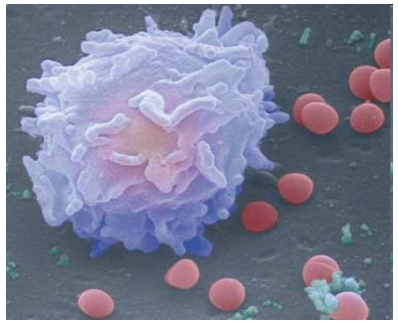


Ochando et al Transplant Intern 2019

Cellules souches mésenchymateuses (MSC) et immunotolérance

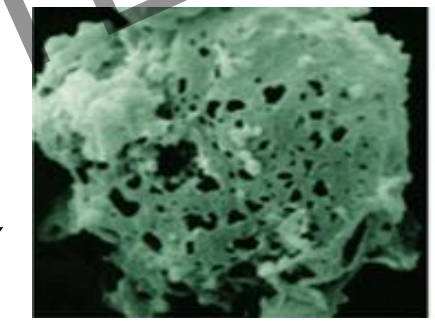
Les cellules souches mésenchymateuses peuvent sécréter une grande variété de facteurs de croissance et de cytokines

Ces facteurs peuvent influencer la tolerance immune et la régénération tissulaire

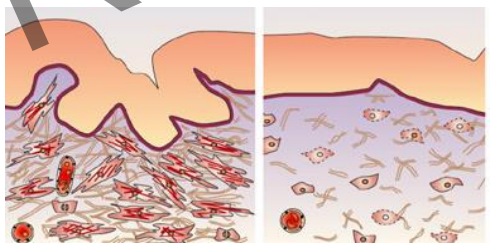


Anti-inflammatory effect

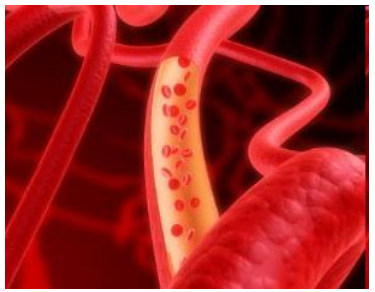
PARACRINE EFFECTS



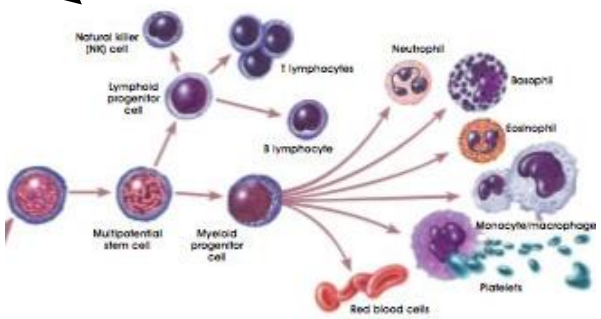
Anti-apoptotic effect



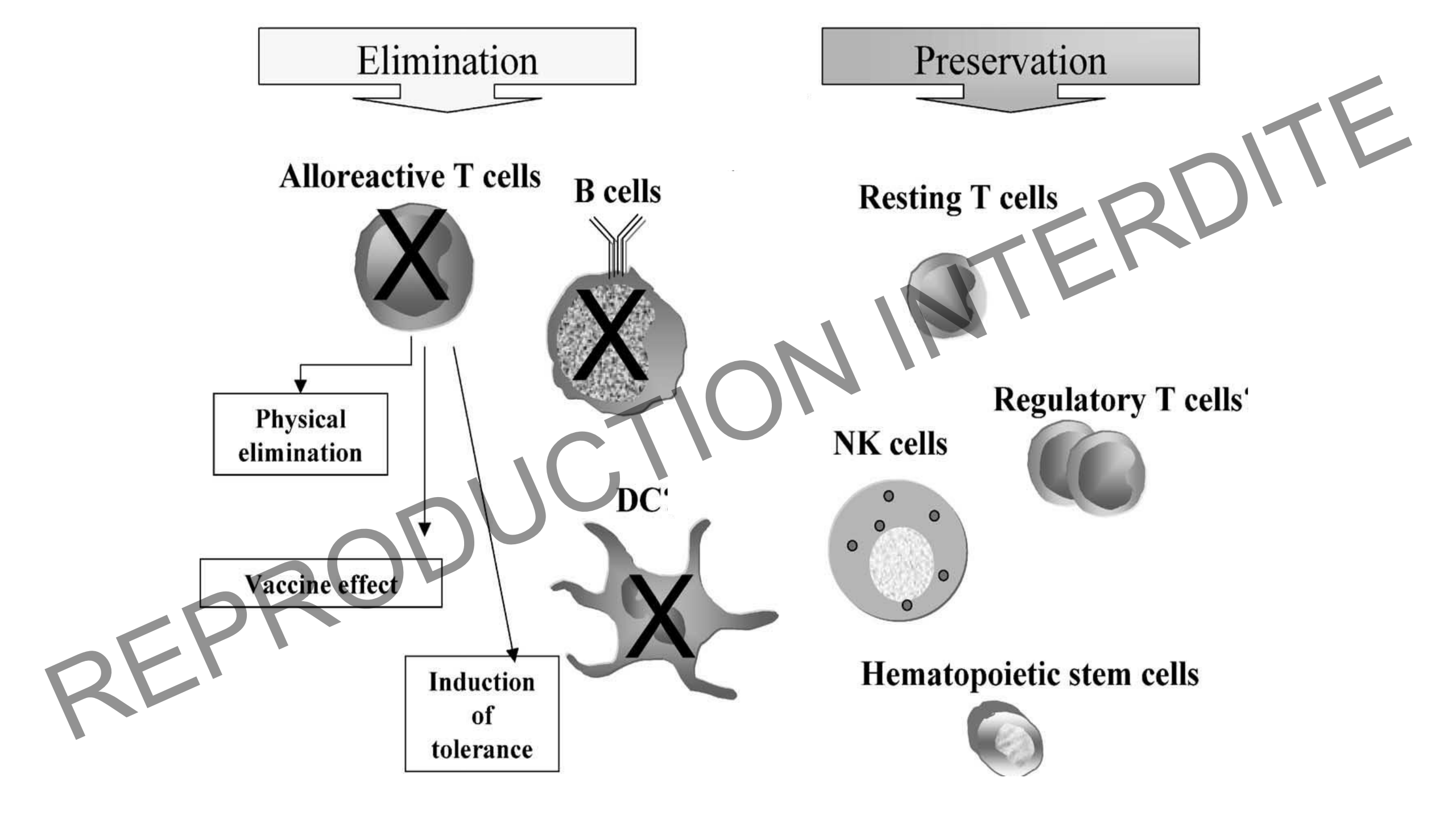
Tissue remodelling



Neo vascularisation

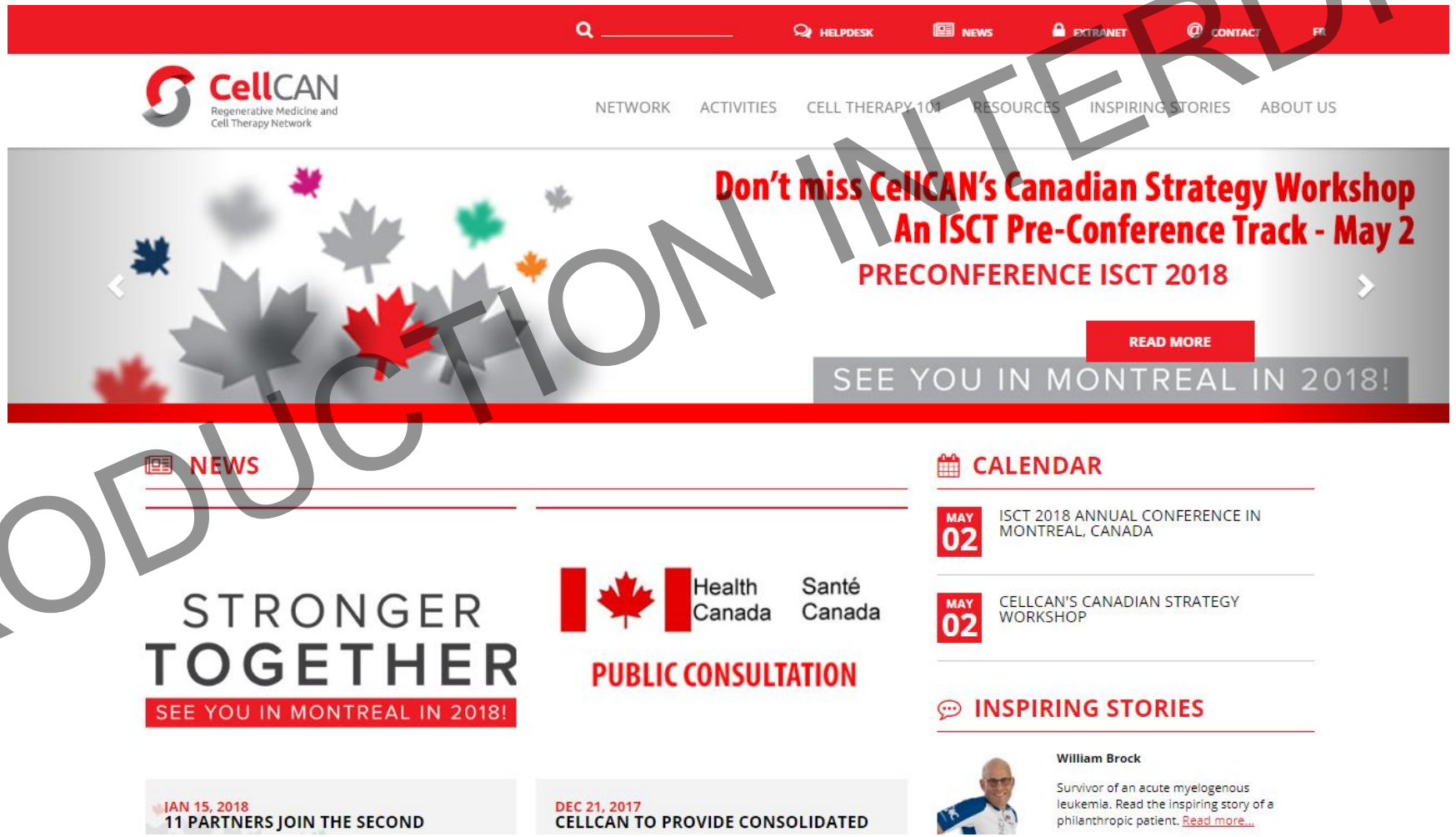


Activation of local progenitor cells



CellCAN WEBSITE

Ilovestemcells.ca
Jaimelescellulessouches.ca



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Unité de Recherche Clinique

Focussing on Cancer and Immunotherapy

Innovation et Commercialisation

Investing in innovative cancer immunotherapies, asset development & commercialization

Organisation de Recherche à Contrat (CRO)

Supporting research projects, including innovative investigator-initiated trials

Translation from bench to clinic | Large Network of Investigators | Regulatory Expertise | In-house development of biomarkers | On Site cGMP facility | Efficient Clinical Trial Implementation | Business Oriented Team | Venture Capital Investment

1 employé en 2016 → 45 employés en 2019

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•<u>Clinical transplant teams</u>

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IRSC CIHR
Instituts de recherche en santé du Canada
Canadian Institutes of Health Research

BioCanRx
Biotherapeutics for Cancer Treatment
Biothérapies pour le traitement du cancer

C3i Centre for Commercialization of Cancer IMMUNOTHERAPY

CellCAN
Regenerative Medicine and Cell Therapy Network

Fonds de la recherche en santé Québec

Cell
ThéCell: Le réseau de thérapie cellulaire et tissulaire du FRQS

HMR Hôpital Maisonneuve-Rosemont Centre affilié à l'Université de Montréal

GenomeCanada