



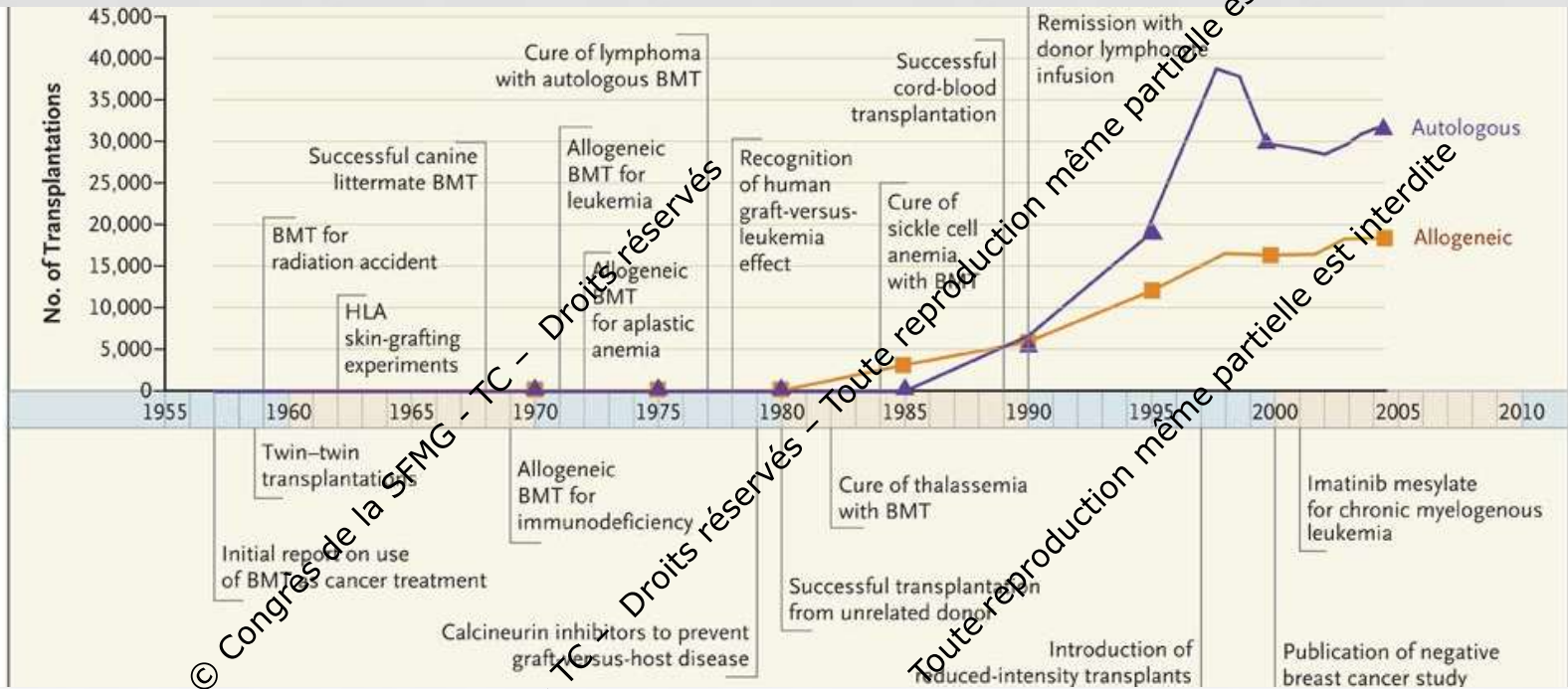
G. Socié, Hématologie / Greffe Hôpital St Louis



Immunobiology of HSCT: Past , present & future

GvHD
a & c
GvL
ID
...

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Droits réservés - Toute reproduction même partielle est interdite

Droits réservés - Toute reproduction même partielle est interdite



APPELBAUM FR. N ENGL J MED 2007;357:1472-1475.

Bone Marrow Transplantation from Bench to Bedside

Ann N Y Acad Sci. 1995;770:34-41.

Historical Review

Br J Haematol. 1999;105:330-39.

Historic Landmarks in Clinical Transplantation: Conclusions from the Consensus Conference at the University of California, Los Angeles

World J Surg. 2000;24:834-43.



D Thomas

IMMUNOLOGY

Failure to transfer Sensitivity to Skin Homografts by Means of 'Immune' Lymphoid Cells in Diffusion Chambers

The H-Y Transplantation Antigen: A Y-linked or Sex-influenced Factor?

Billingham; *Nature* 1966 & 1968



R Billingham

1. van Bekkum DW, de Vries MJ. Radiation chimaeras. London: Logos Press, 1967.
2. Billingham RE. The biology of graft-versus-host reactions. Harvey Lect 1966-67; 62:21-78.
3. Gowans JL. The fate of parental strain small lymphocytes in F₁ hybrid rats. *Ann N Y Acad Sci* 1962; 99:32-55.
4. McGregor DD. Bone marrow origin of immunologically competent lymphocytes in the rat. *J Exp Med* 1968; 127:953-66.



D van Bekkum



G Matthé

The Major Histocompatibility Complex in Man

Past, present, and future concepts.

Jean Dausset

SCIENCE, 213, 1981

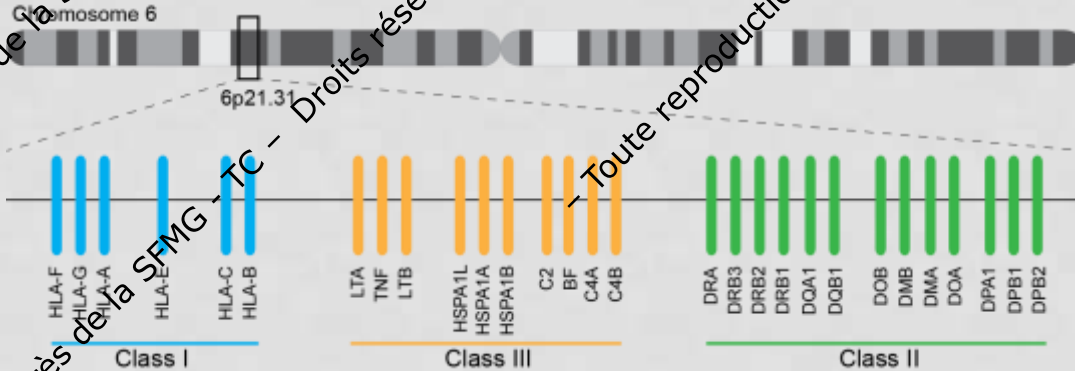


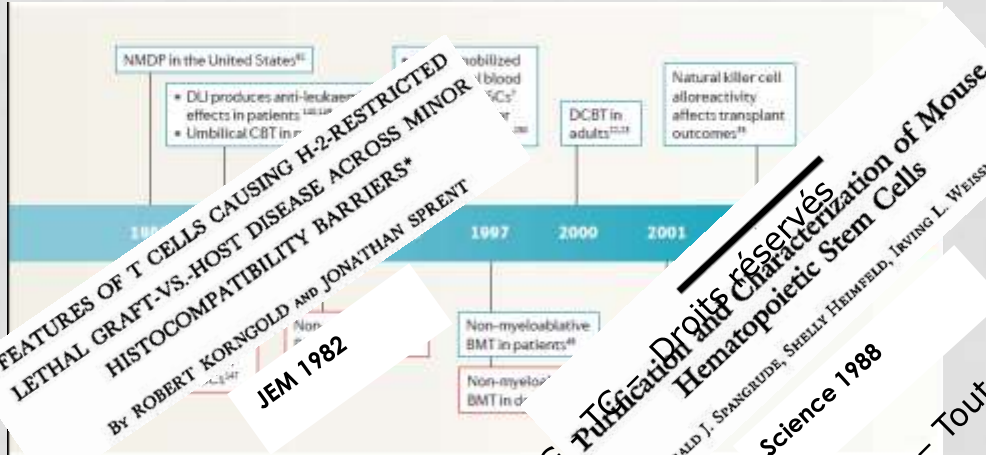
J Dausset



J van Rood

HLA
NIMA /NIPA
Minor H-ag





TIMELINE

Allogeneic haematopoietic stem cell transplantation: individualized stem cell and immune therapy of cancer

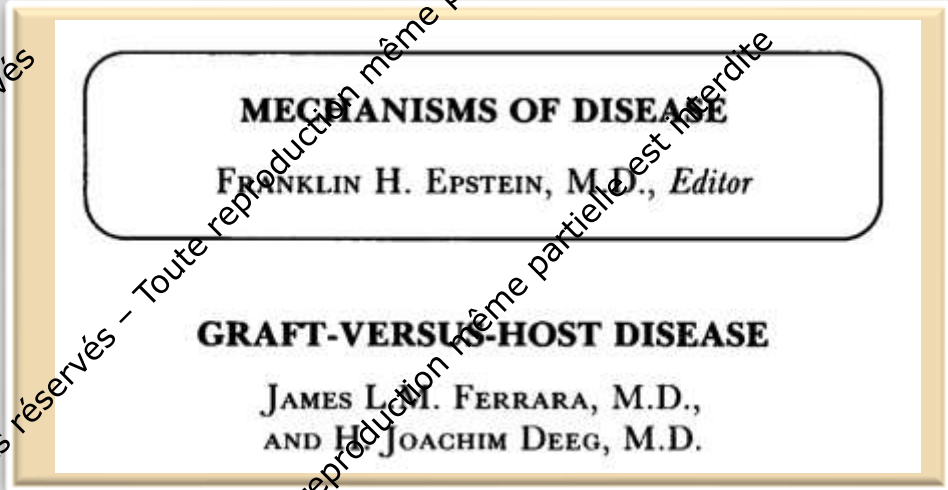
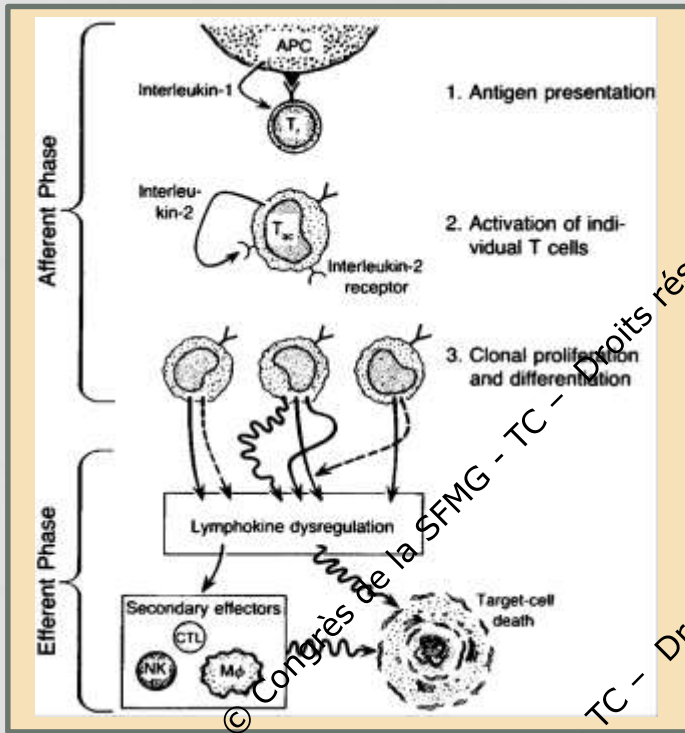
Robert R. Jenq and Marcel R. M. van den Brink

Nature Reviews Cancer 2010



Tout reproduction même partielle est interdite

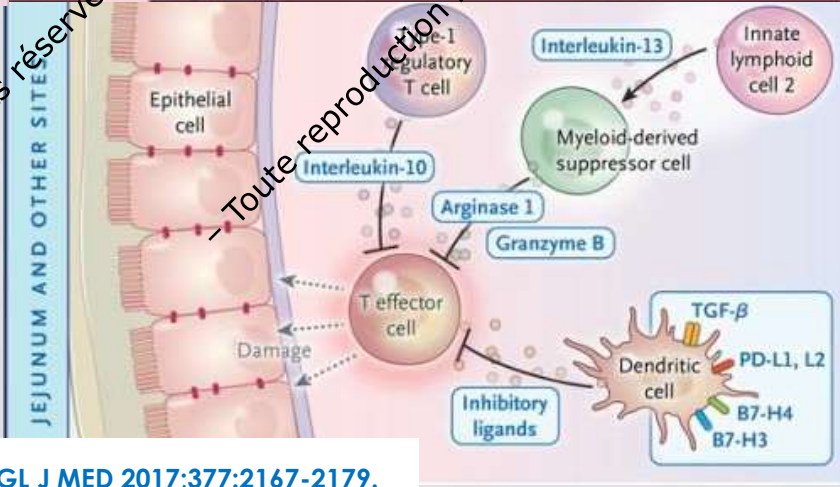
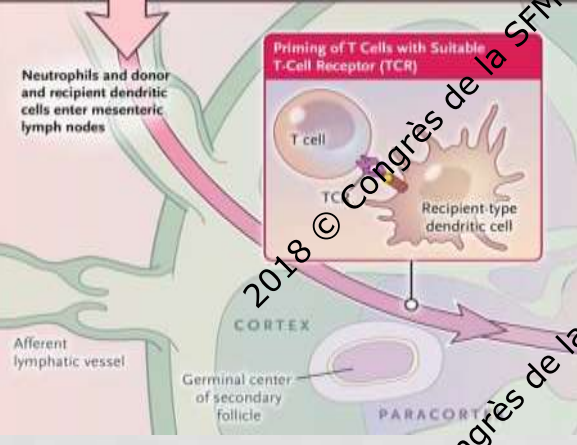
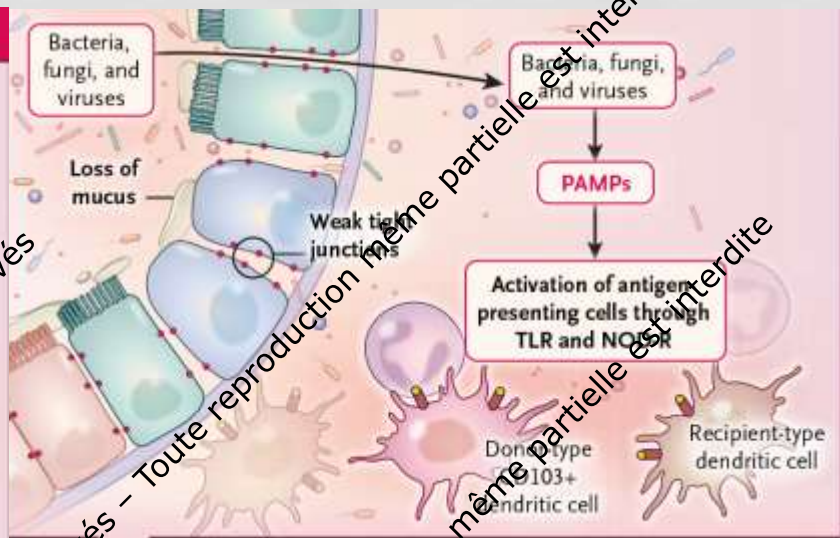
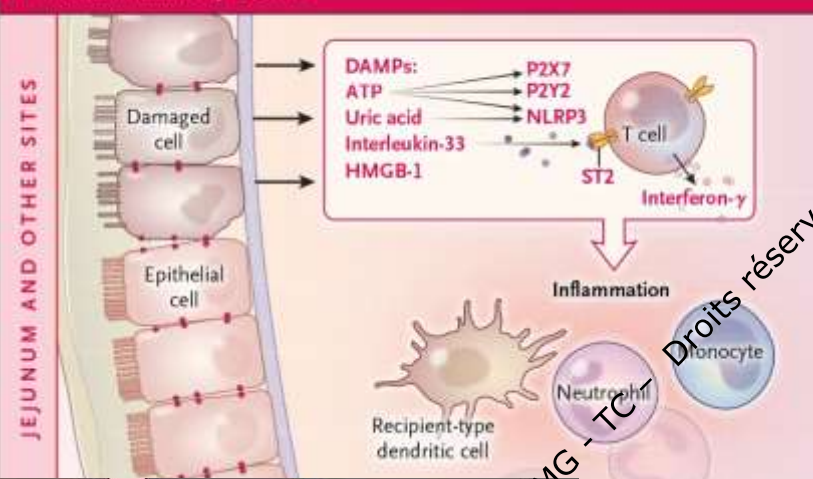
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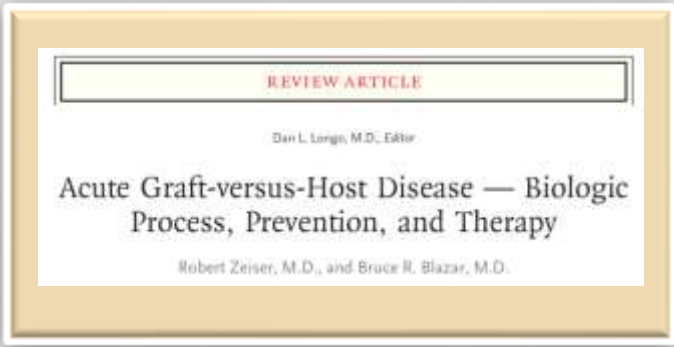


The NEW ENGLAND
 JOURNAL of MEDICINE

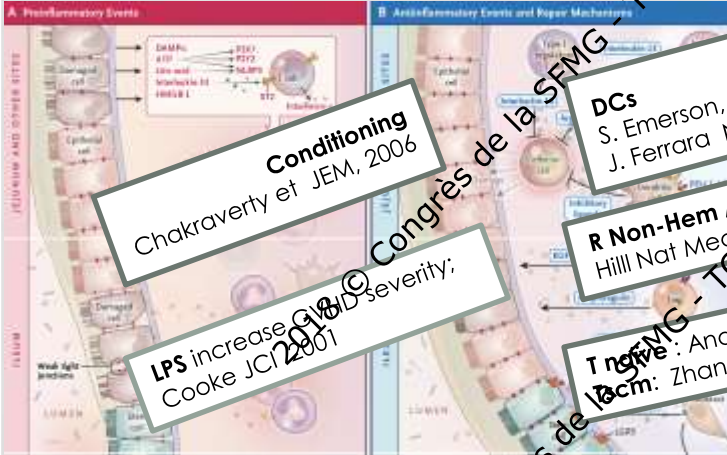
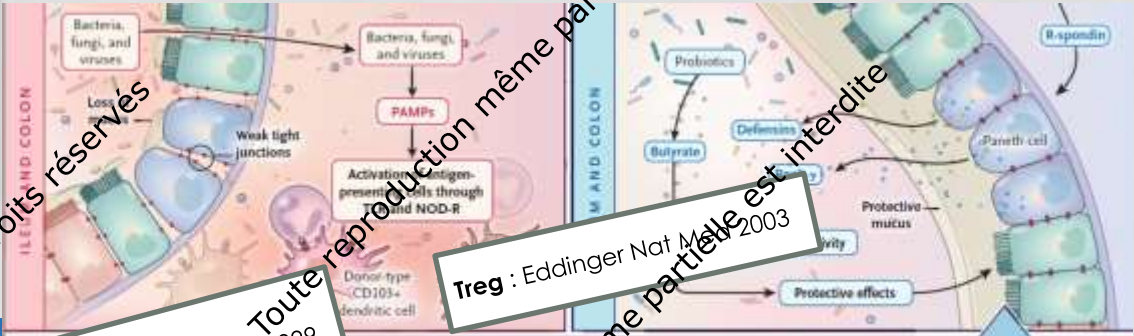
FERRARA JL DEEG HJ. N ENGL J MED 1991;324:667-674.

A Proinflammatory Events





N Engl J Med 2017;377:2167-79.



Conditioning
Chakraverty et JEM, 2006

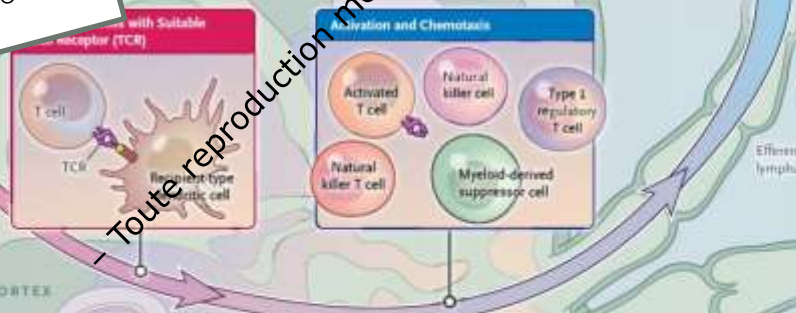
LPS increase GVHD severity;
Cooke JCI 2001

DCs
S. Emerson, W Shlomchick Science 1999
J. Ferrara Nat Med 2002

R Non-Hem APCs
Hilli Nat Med 2012

T reg: Anderson, JCI 2003
T reg cm: Zhang, Nat Med 2005

Treg : Eddinger Nat Med 2003



Chronic GvHD

Review Series

ADVANCES IN HEMATOPOIETIC CELL TRANSPLANTATION

Current issues in chronic graft-versus-host disease

Gérard Socié^{1,2} and Jerome Ritter^{2,3}

Blood 2014; 124: 374-84

Blood 2017; 129: 22-29



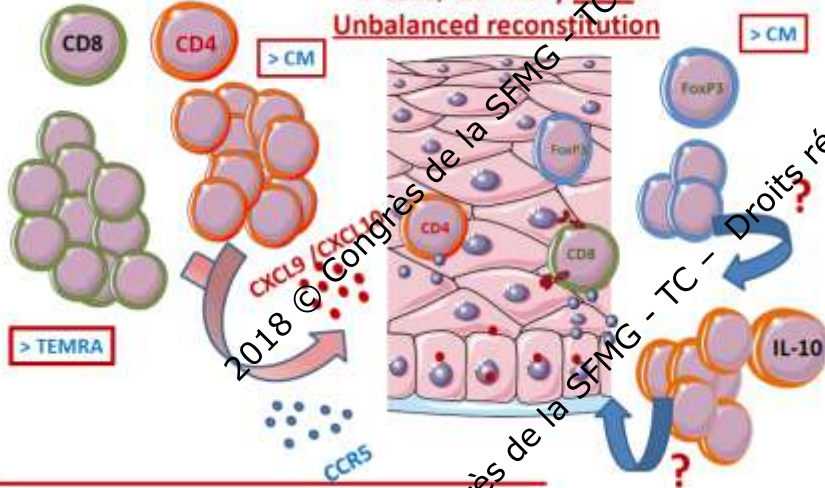
J Ritter



Sarantopoulos

T-cells; summary 2018

Unbalanced reconstitution



B-cells; summary 2018

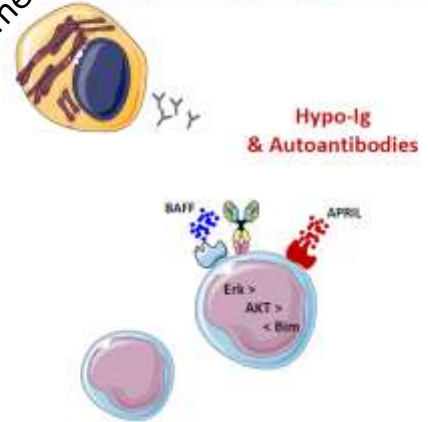
cGVHD-associated immune deficiency; pathogenicity?

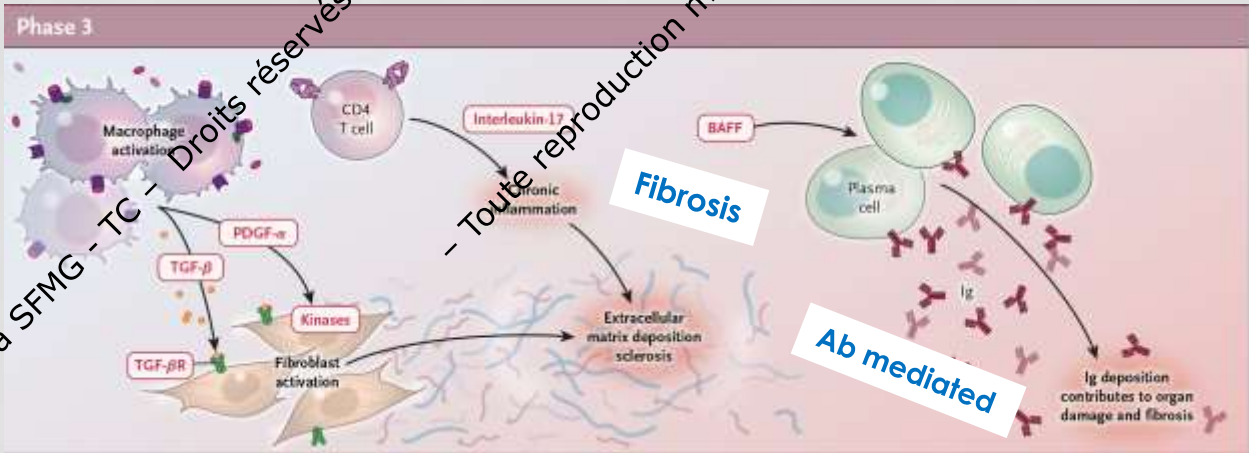
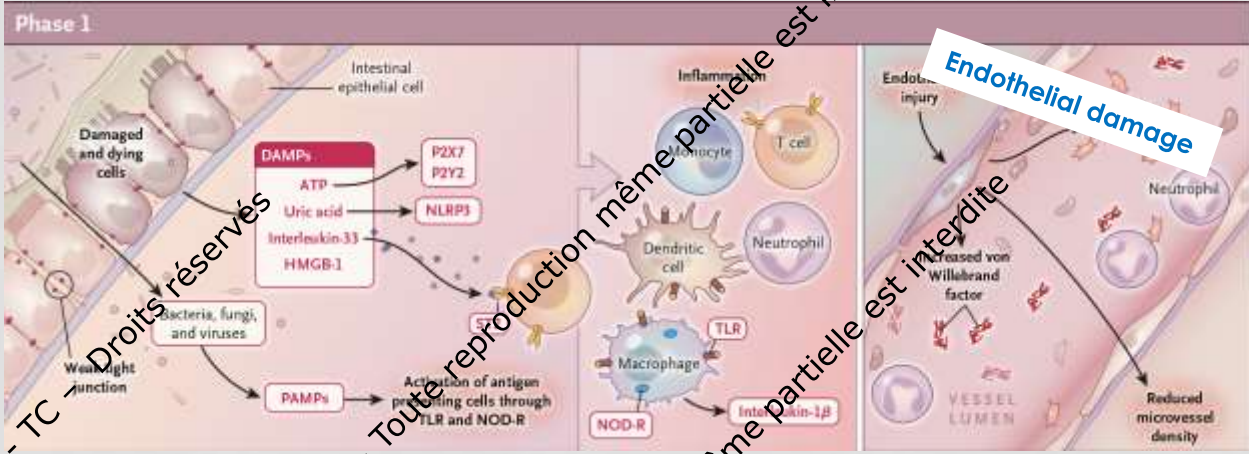
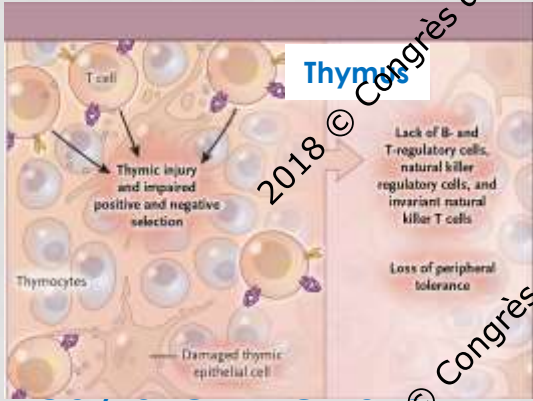
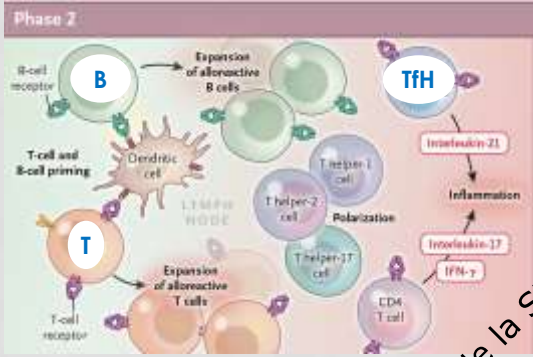
Increased transitional
"pre-germinal" B cells
CD24^{hi} CD38^{hi} IgM+CD21-

Decreased B1 like
CD20+CD27+CD43+CD70-

Decreased Treg
But > IL10 in CD24^{hi}CD27^{hi}CD38^{hi}

Resistance to apoptosis
Increased BCR responsiveness





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GVHD: balance between alloreactivity/ tissue sensitivity with immune/ tissue tolerance

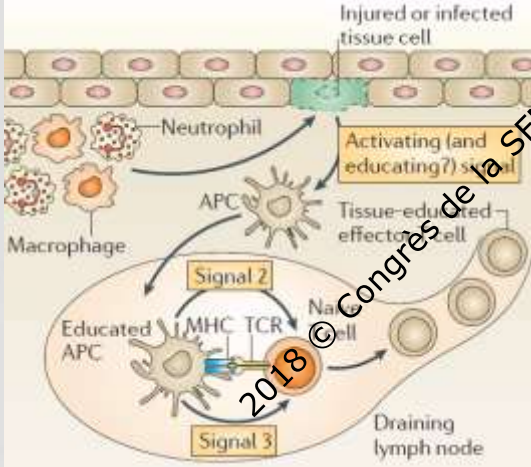


Polly Matzinger

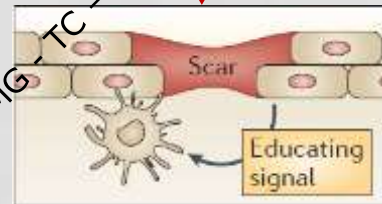
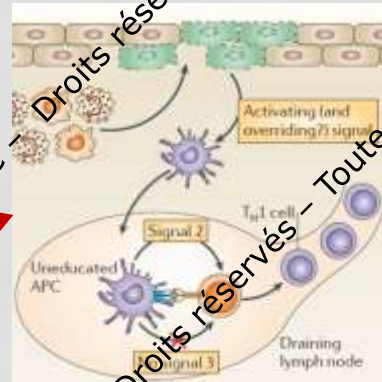
ESSAY

Tissue-based class control: the other side of tolerance

Polly Matzinger and Tirumalai Kamala



NRI 2011

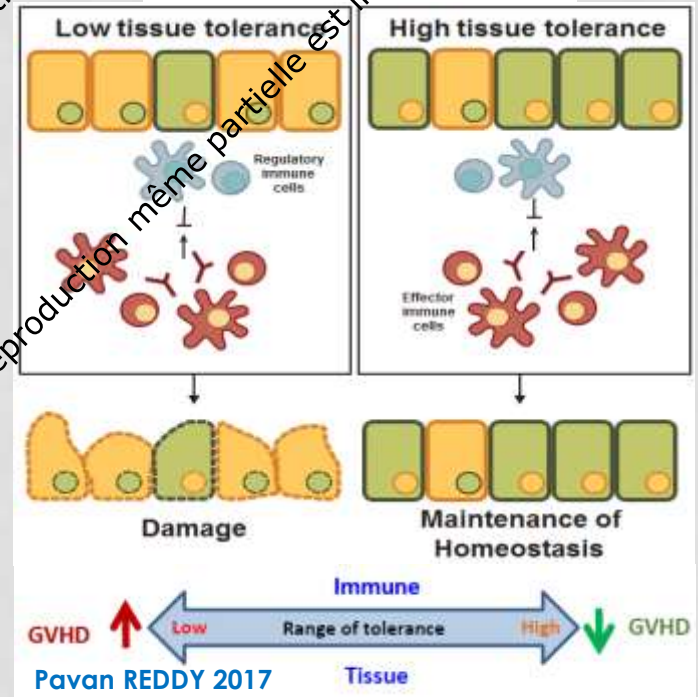


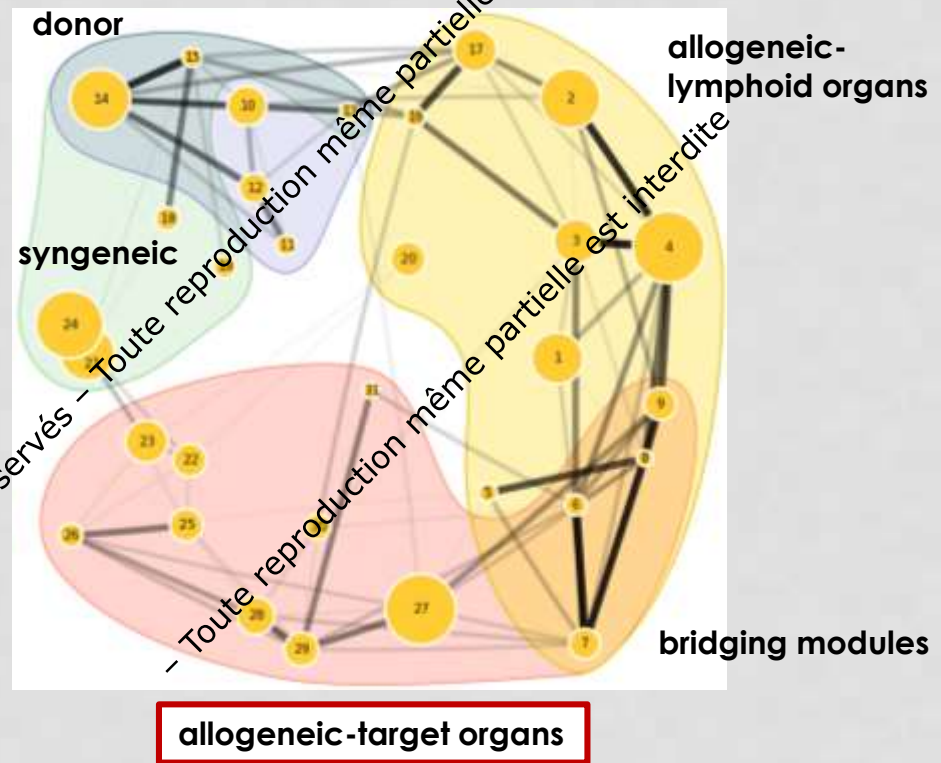
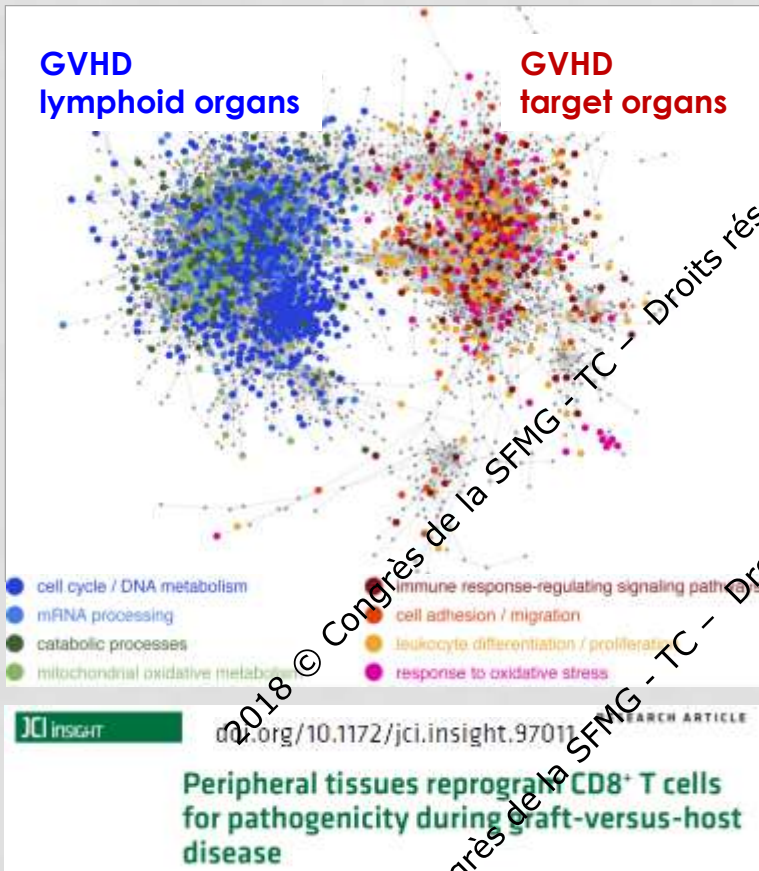
II-22

Immunity 2012: 37: 339-350

R-Spondin

J Exp Med 2017; 208: 285-294





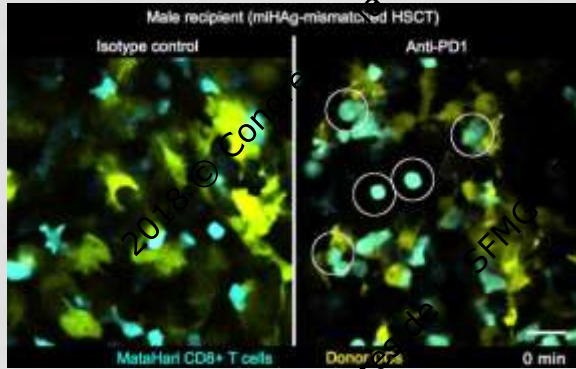
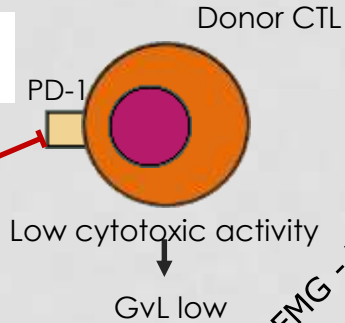
Tissue compartmentalization in acute GVHD

Michonneau D, ... Bousso P;
Immunity, 2016

Lymph node

Tissue environment

PD-L1
PD-L2



Liver

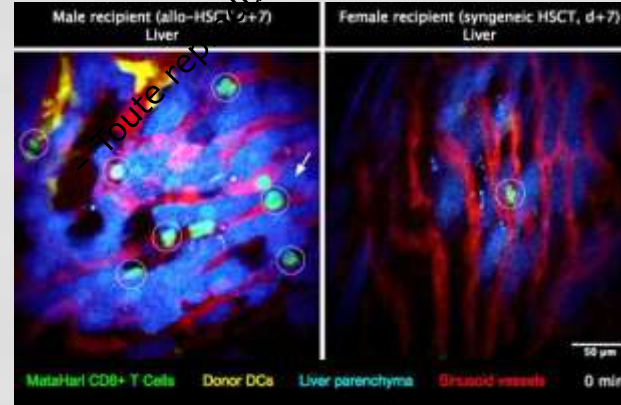
PD-1

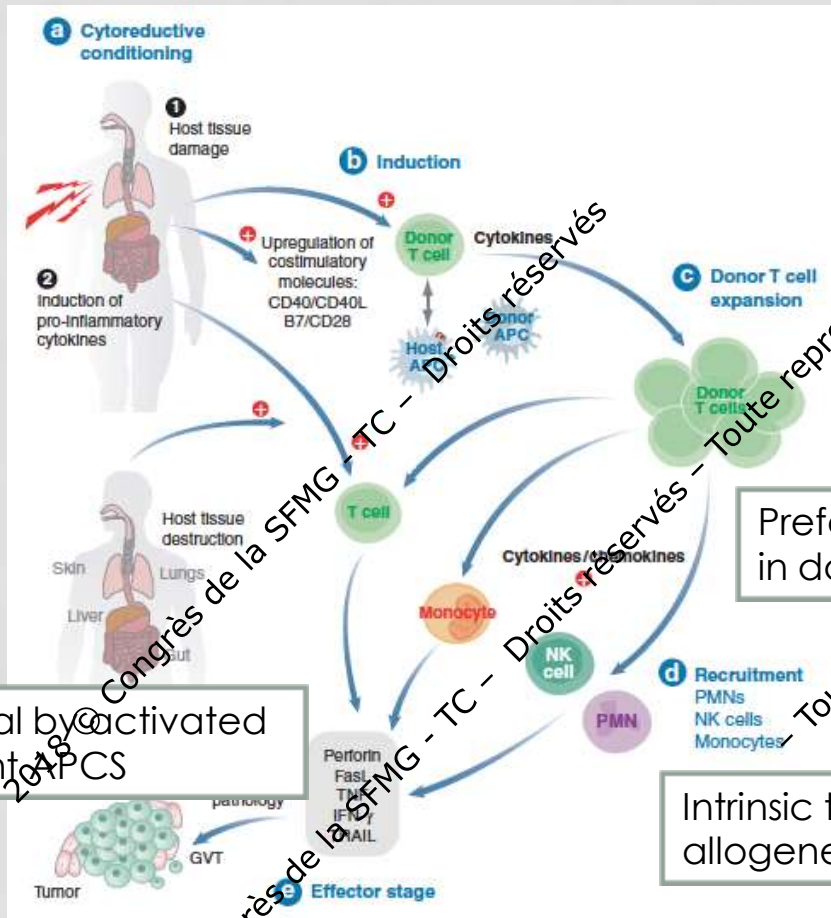
Donor CTL

High cytotoxic activity

Tissue damages (GVHD)

GvL efficacious





GVHD's paradigm :

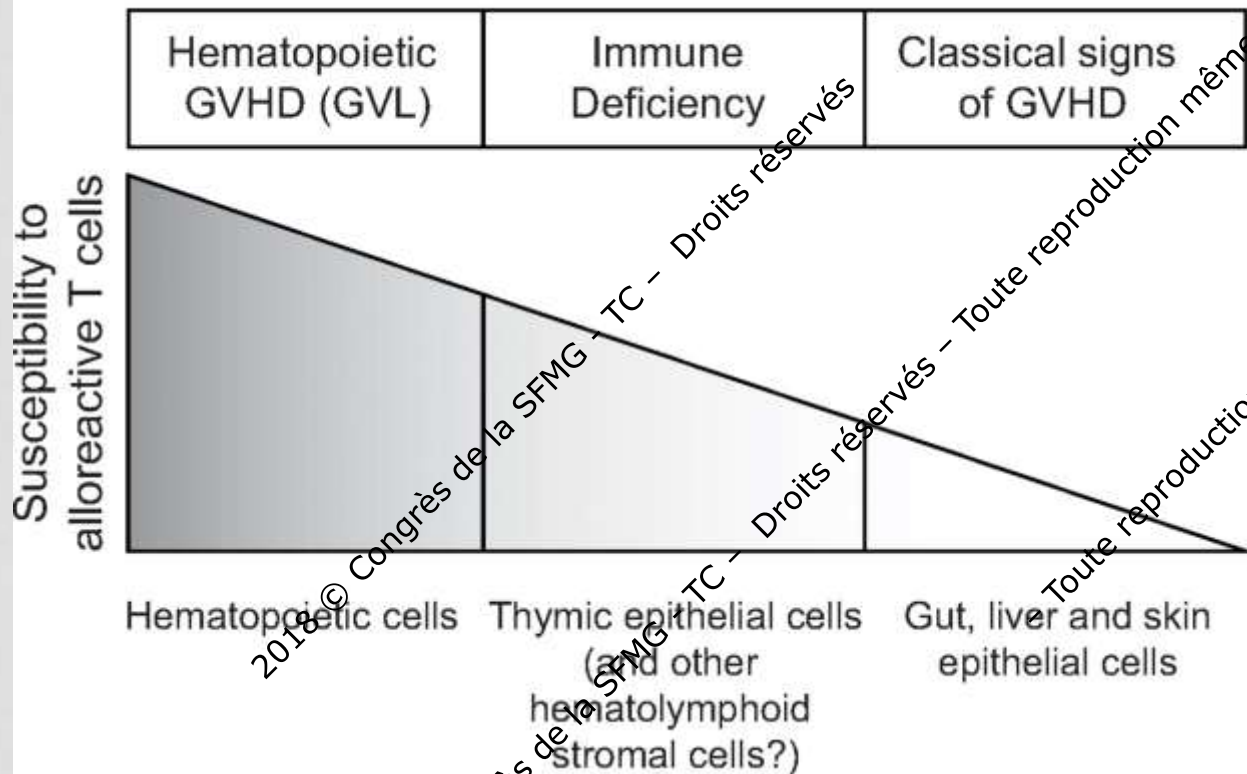
- mHSA and HLA are ubiquitously expressed
- Acute GVHD mainly affects skin, GI & liver

Preferential T cell migration in damaged tissues

Intrinsic tissue sensitivity to allogeneic T-cells

Second signal by activated tissue resident APCs

Clinical impact



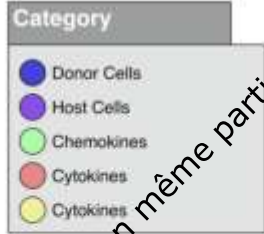
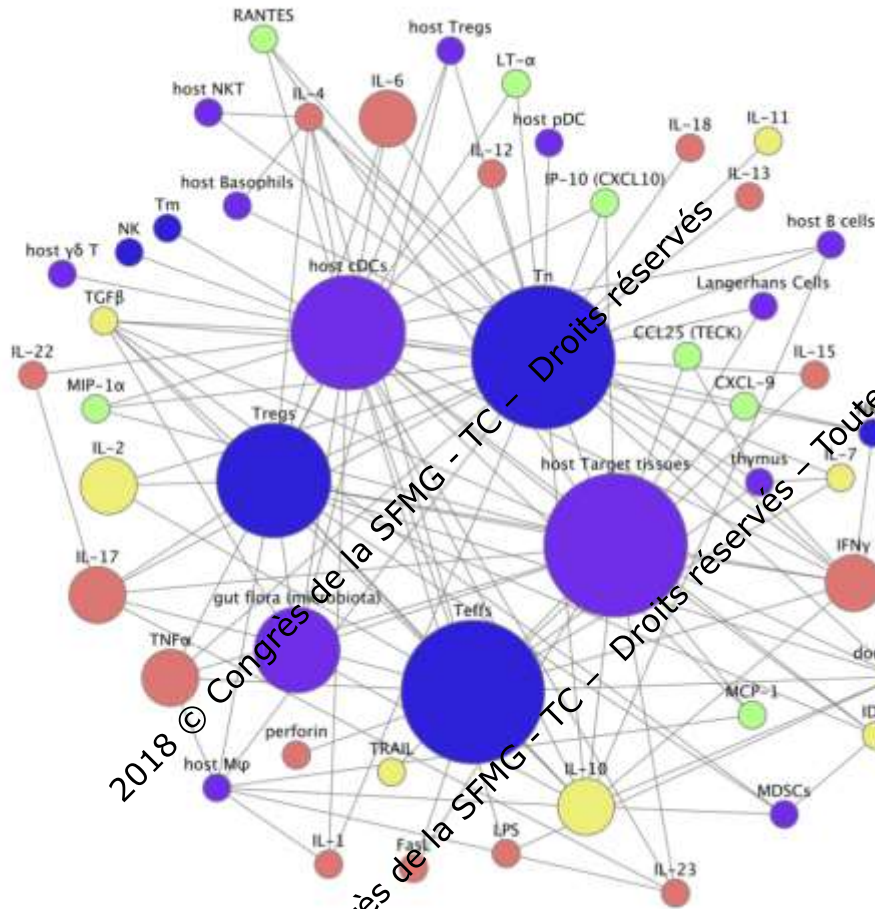
© Perreault



Blood 2011;118:2951-2959

Perspectives

Next-generation leukemia immunotherapy



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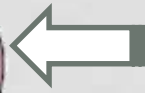
Toute reproduction même partielle est interdite

- Bottom-up
- Dynamic
- Multi-scalar
- Modular
- Interactive
- Comprehensible

P. Reddy

Acute GVHD pathophysiology From mice to Human

Chronic GVHD pathophysiology From Human to mice



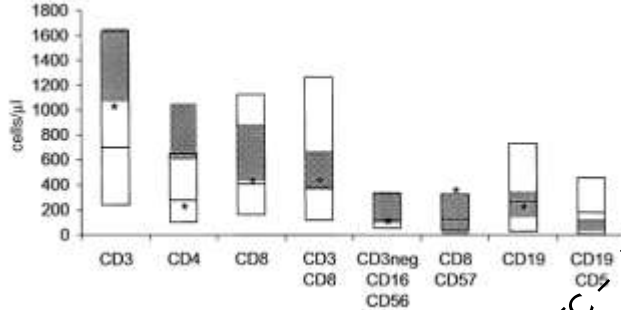
Why ?

Not inbred
Not germ free
With Chemo/TBI
Age
Donor
GvHD prophylaxis
...

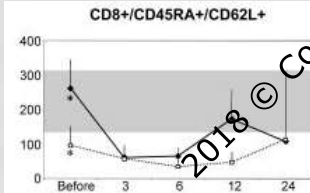
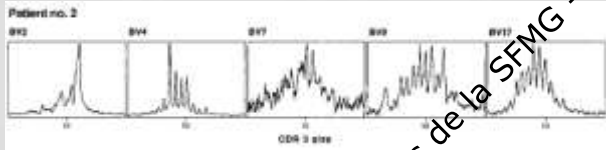
Pathology; **single time point**; double vs. multicolor; Treatment ? +++
Cytokines / Chemokines; **plasma** ELISA vs. Q-PCR **tissue** +++
Flow cytometry; Cell numbers ++, **PB vs. tissue**
Proteomics; urine vs. tissue
Genomics; SNPs, Expression array...; Cell numbers +++ ;
Population homogeneity

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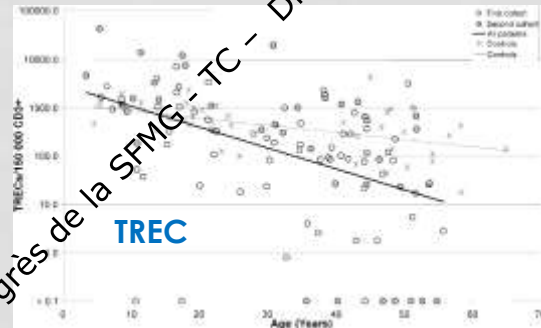
Br J Haematol 2001, 115: 630-641



Hôpital Universitaires
SAINT-LOUIS
LARIBOISIÈRE
FERNAND-WIDAL

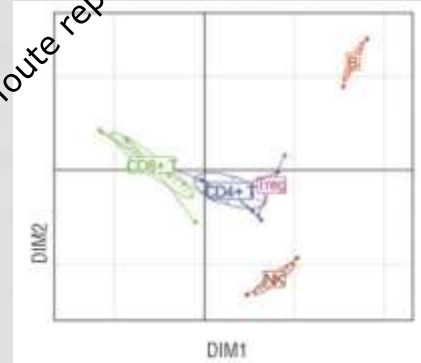
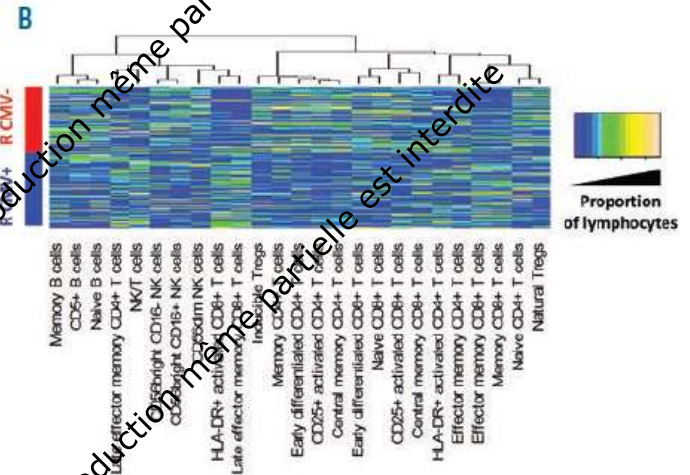


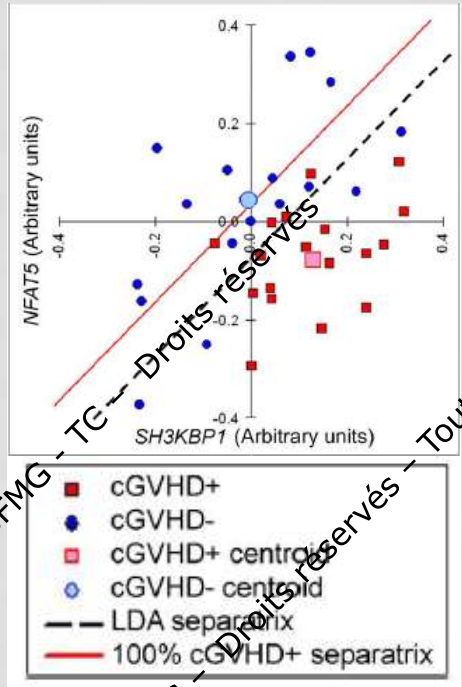
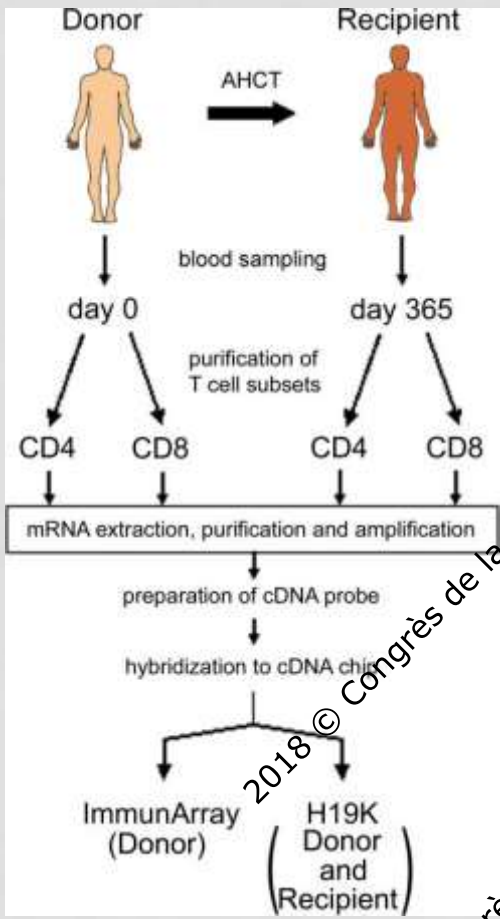
Blood 2005;105: 2608-2613
Blood 2002;99:1458-1464



TREC

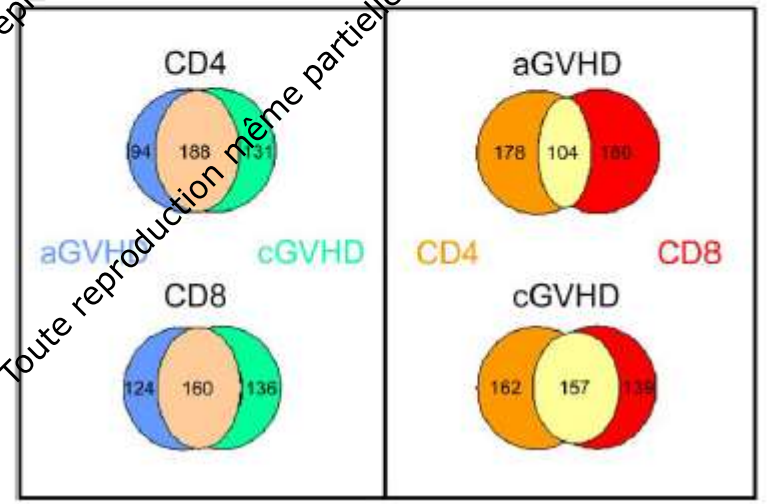
Haematologica 2015; 100(1): 114-23



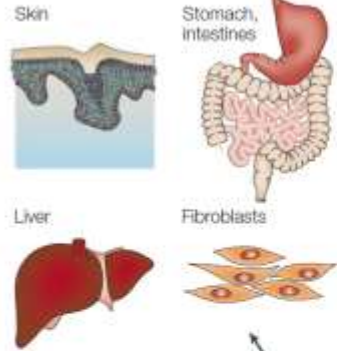


A

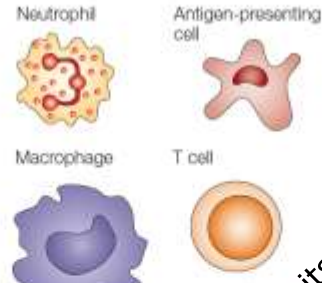
DNA Chip	CD4		CD8	
	aGVHD	cGVHD	aGVHD	cGVHD
ImmunArray	88	76	110	69
H19K	194	243	174	227



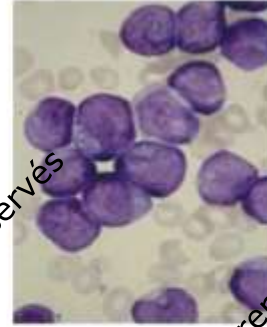
Epithelial tissues



Haematopoietic system

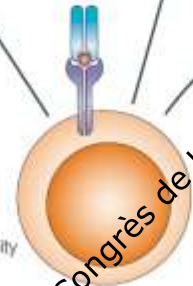


Leukaemia



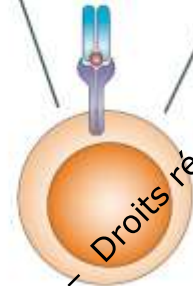
GVHD

T cell responding to broadly expressed minor histocompatibility antigen

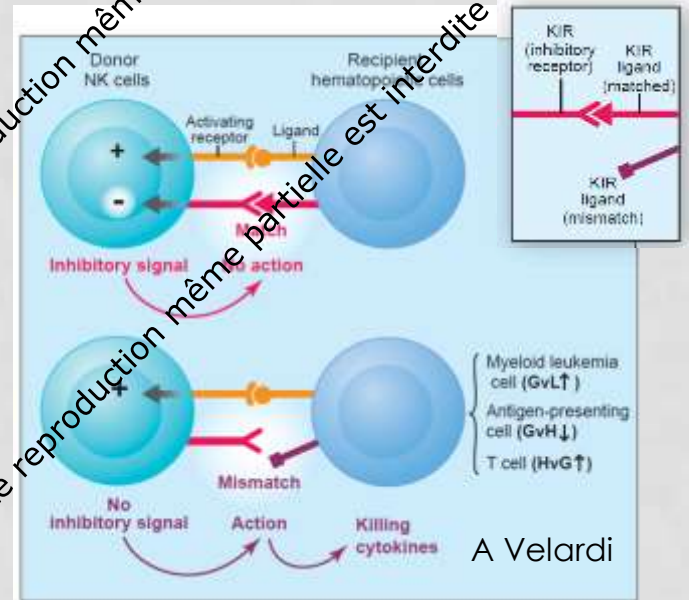


GVL

T cell responding to haematopoietic-restricted minor histocompatibility antigen



GVL



A Velardi



S Riddell

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↑ Initiation

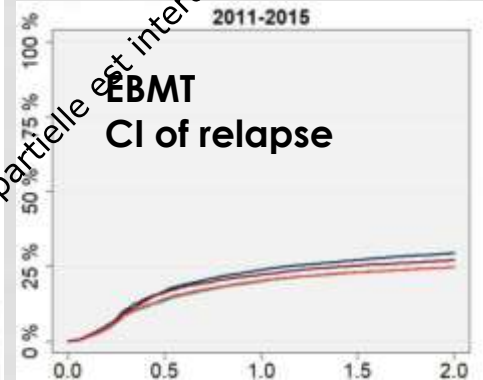
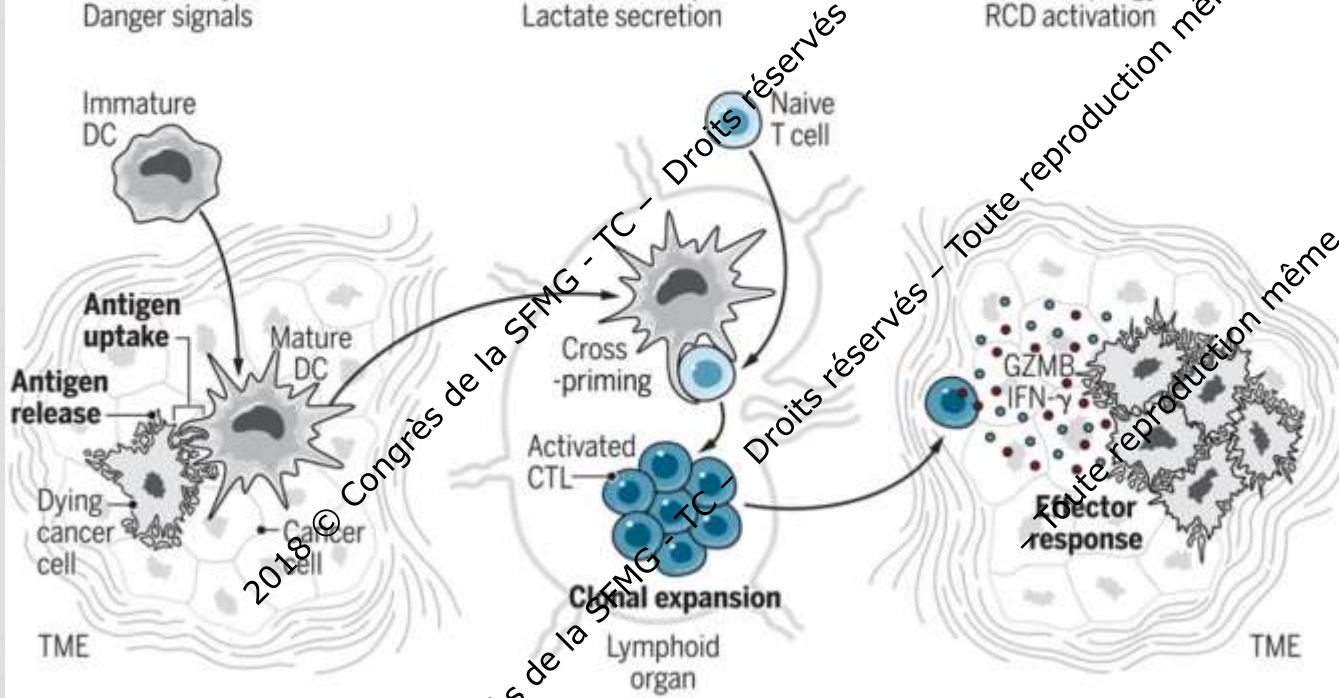
Mutational load
TNA quantity
Viral mimicry
Danger signals

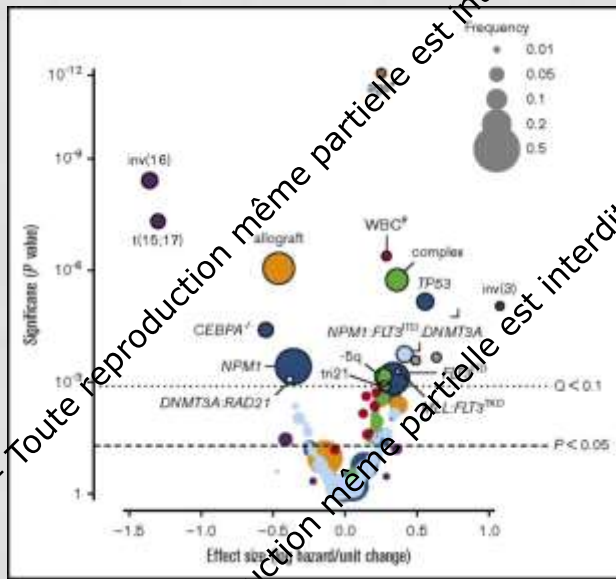
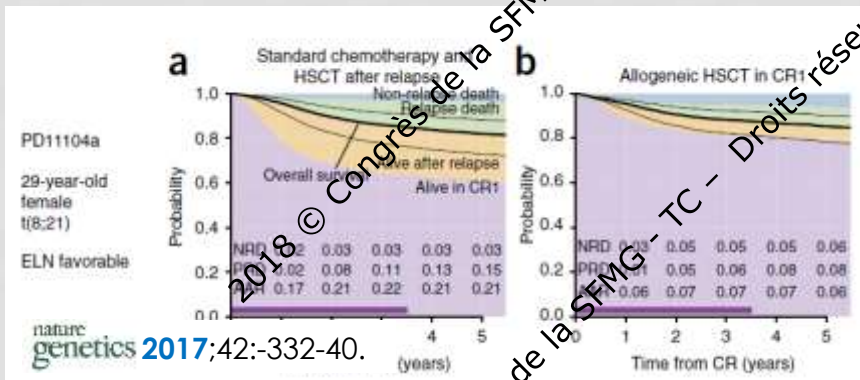
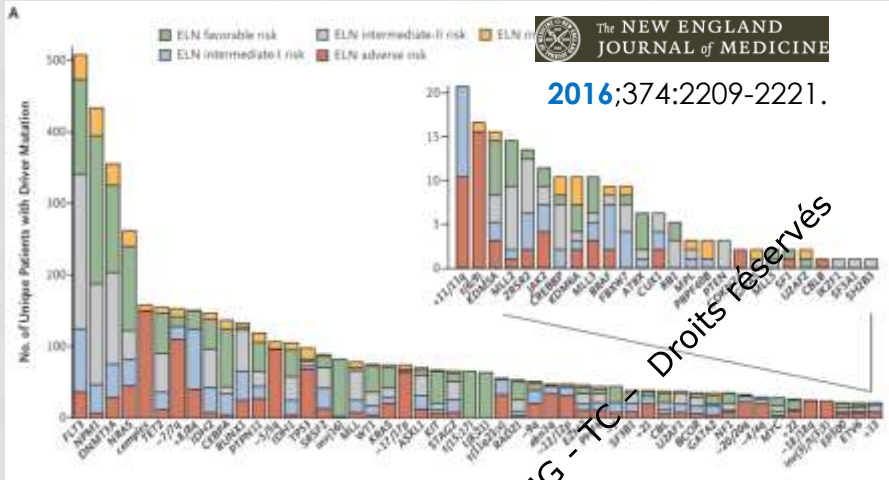
✗ Regulation

Co-inhibitory ligands
Immunosuppressive factors
Metabolic competition
Lactate secretion

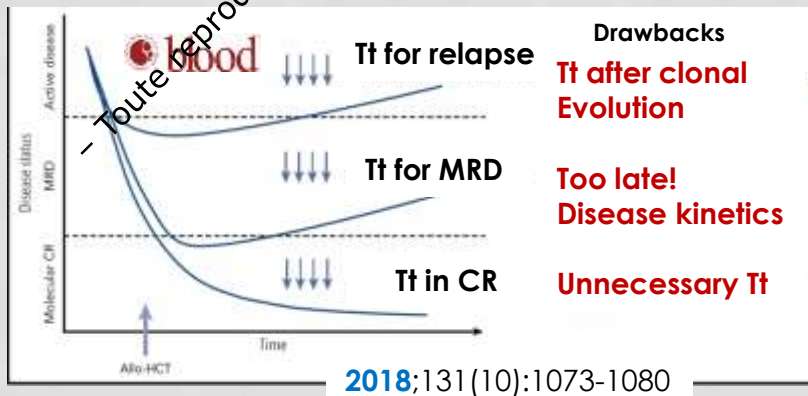
↑ Execution

Antigen presentation
IFNGR signaling
Low autophagy
RCD activation

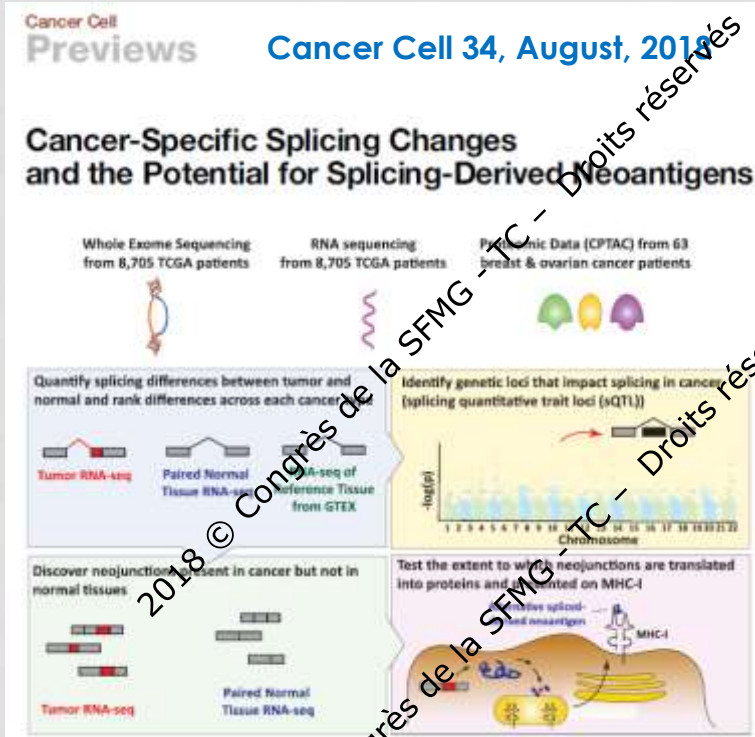




blood advances
 2018;2:3070-3080

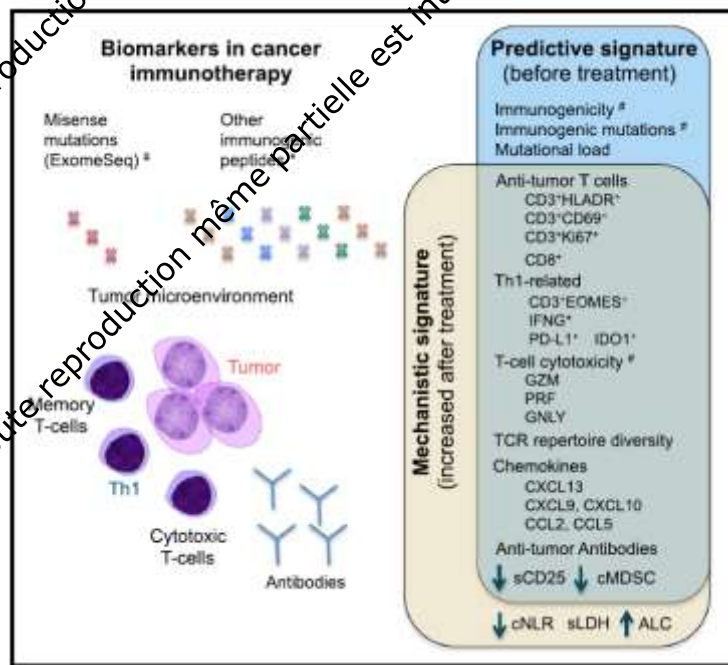


LSA; Leukemia specific antigens; ?? Even for *bcr-abl*
LAA; Leukemia associated antigens; PR1 (CML), WT1
miHA; minor Histocompatibility Ags; HY, HA1-8, HB1 ...

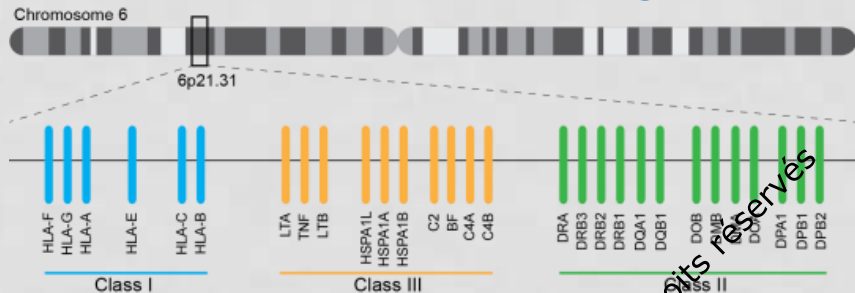


Tumor Microenvironment and Immunotherapy: The Whole Picture Is Better Than a Glimpse

Immunity 2015, October 20, 2015 © 2015 Elsevier Inc. 631

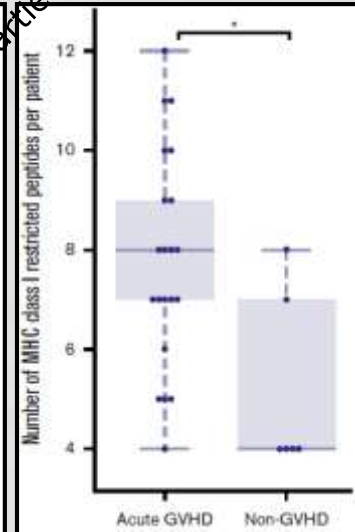
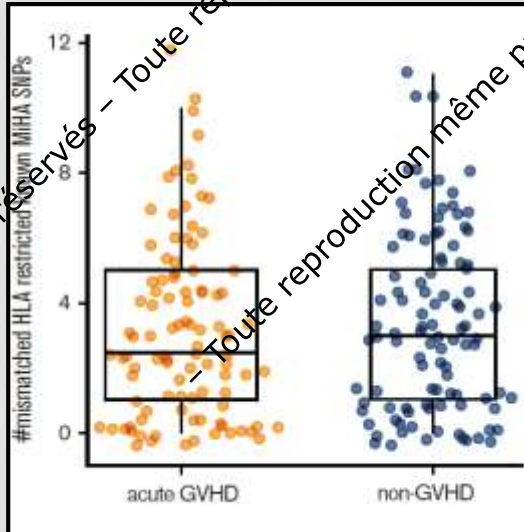
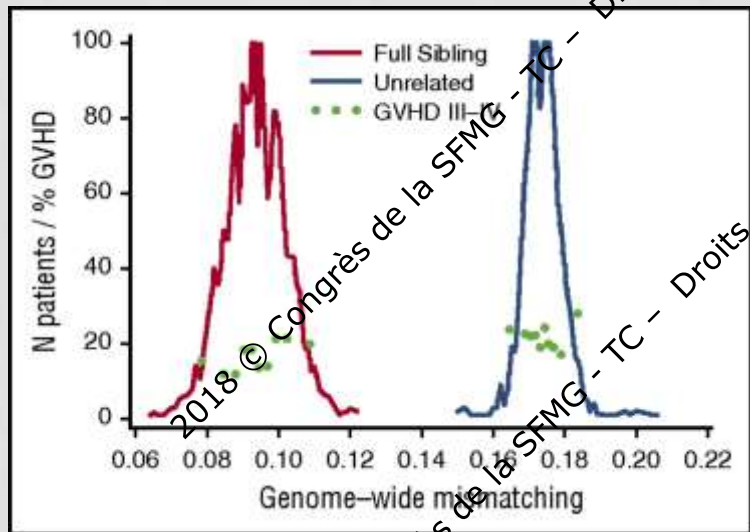


HLA & Non-HLA immunogenetics



Immunogenetics in
10/10 Allele matched UD
Lessons from
Genome wide associations

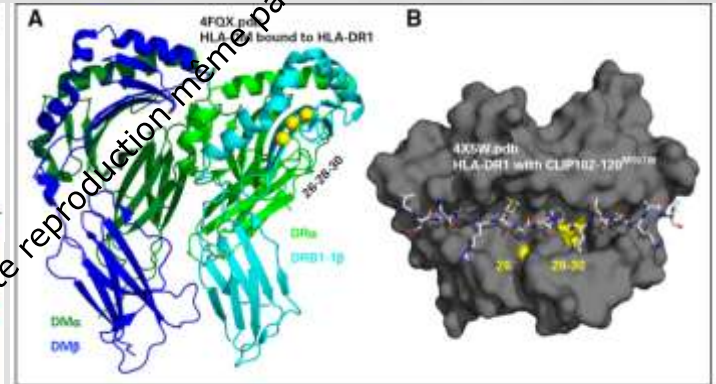
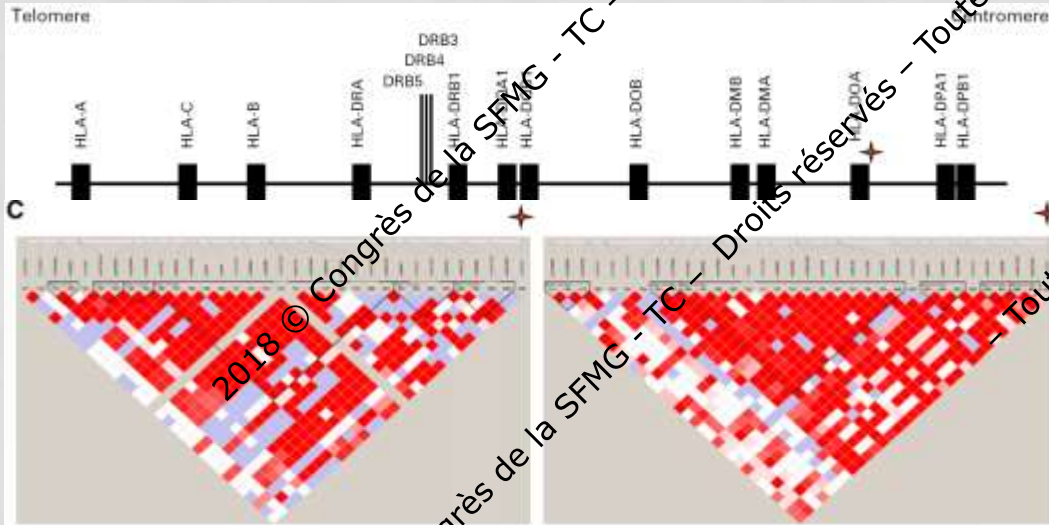
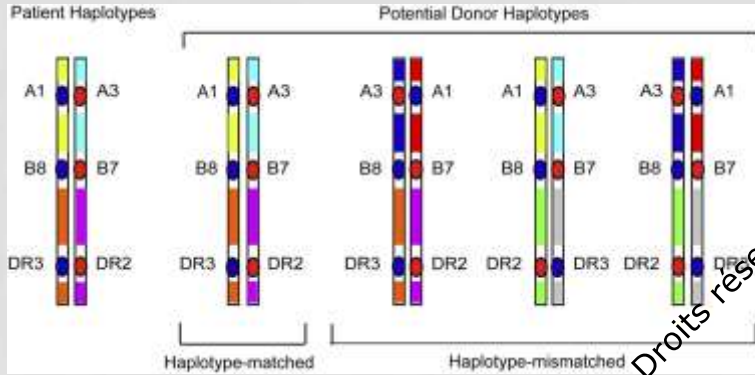
Non permissive DP > HY > miHA



Martin et al. Blood 2017;129:791-798
W Wang et al. Blood Advances 2018;19:2419-2429

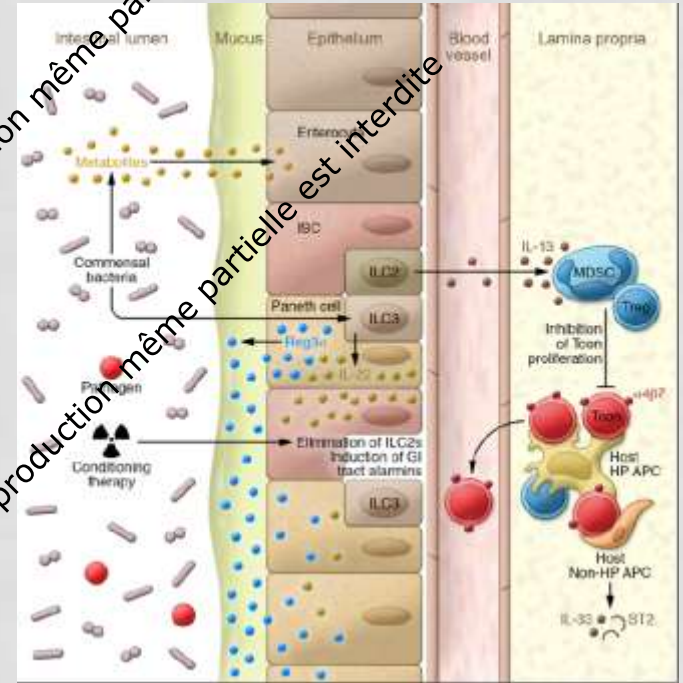
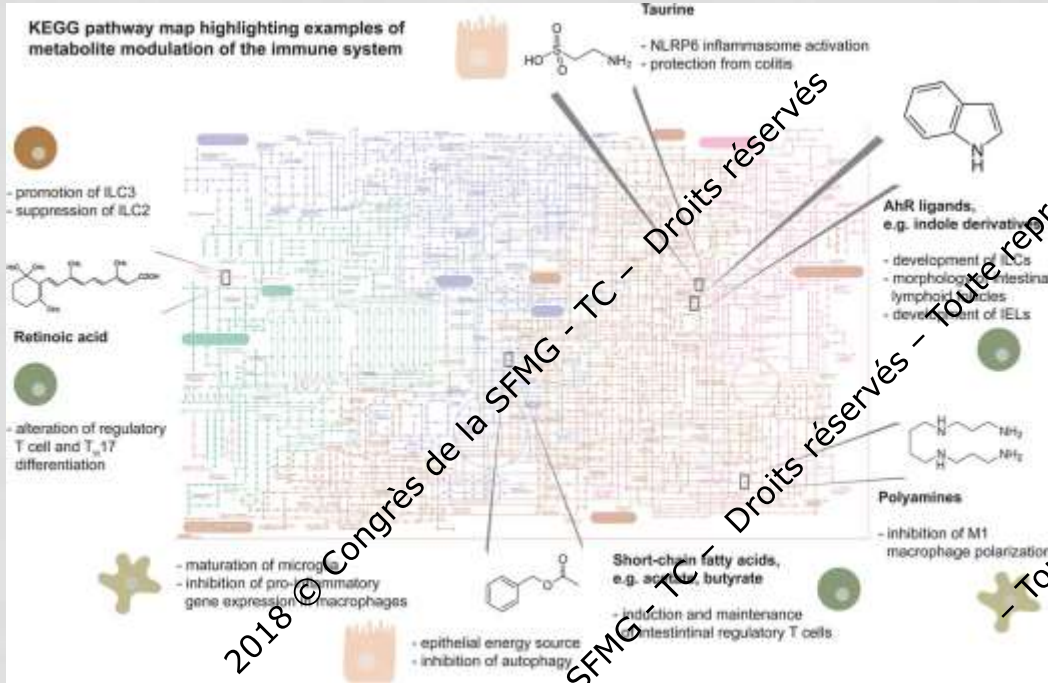
Patient HLA Germline Variation

The susceptibility variants are linked on patient haplotypes that span ~500,000 base pairs and involve genes responsible for **antigen & processing (HLA-DOA)** & **presentation HLA DRB-1**



E Pettersdorf

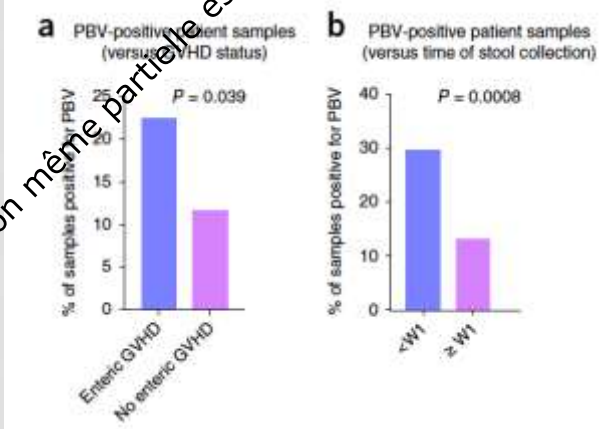
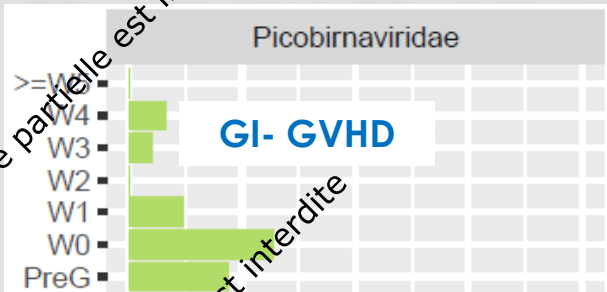
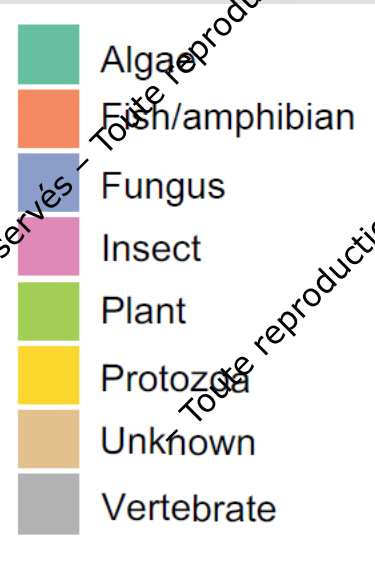
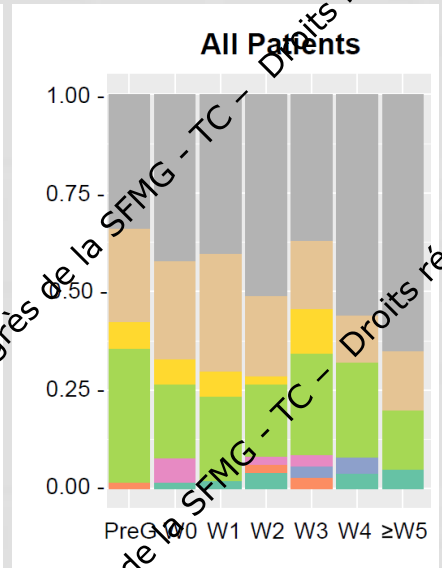
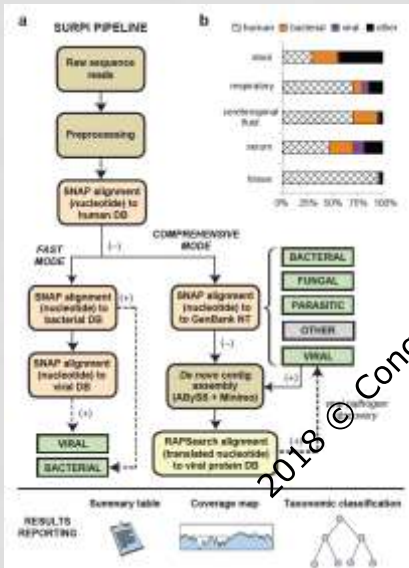
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In a time dependent Cox model Picobirnaviruses were predictive of enteric GvHD stage ≥ 2 HR = 2.66 [1.46;4.86] of any type of GvHD HR = 1.75 [1.07;2.865]

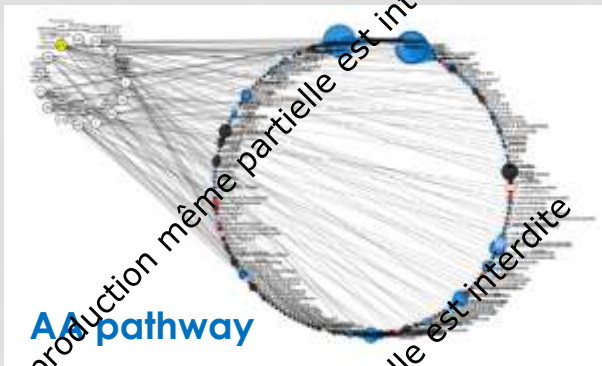
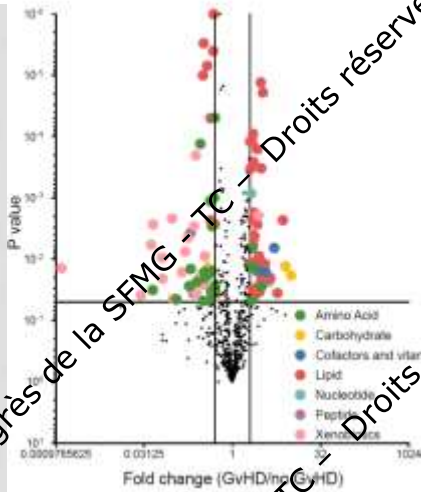
Median 2.9×10^7 reads per sample





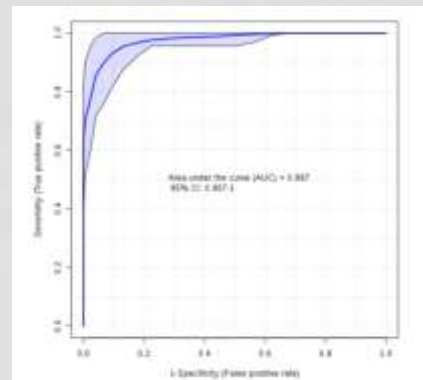
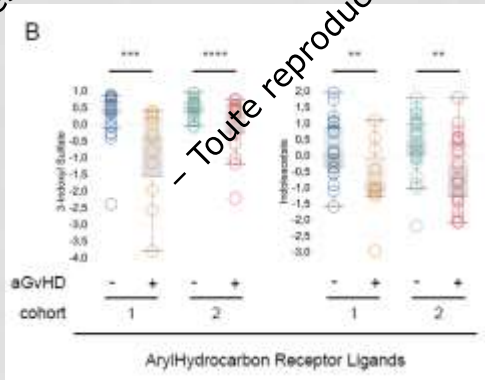
P REDDY

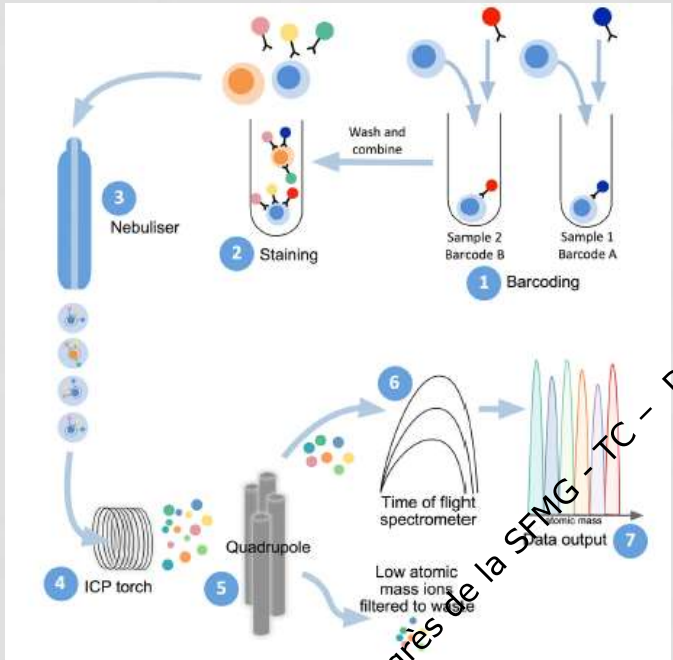
Gut microbiome-derived metabolites modulate intestinal epithelial cell damage and mitigate graft-versus-host disease



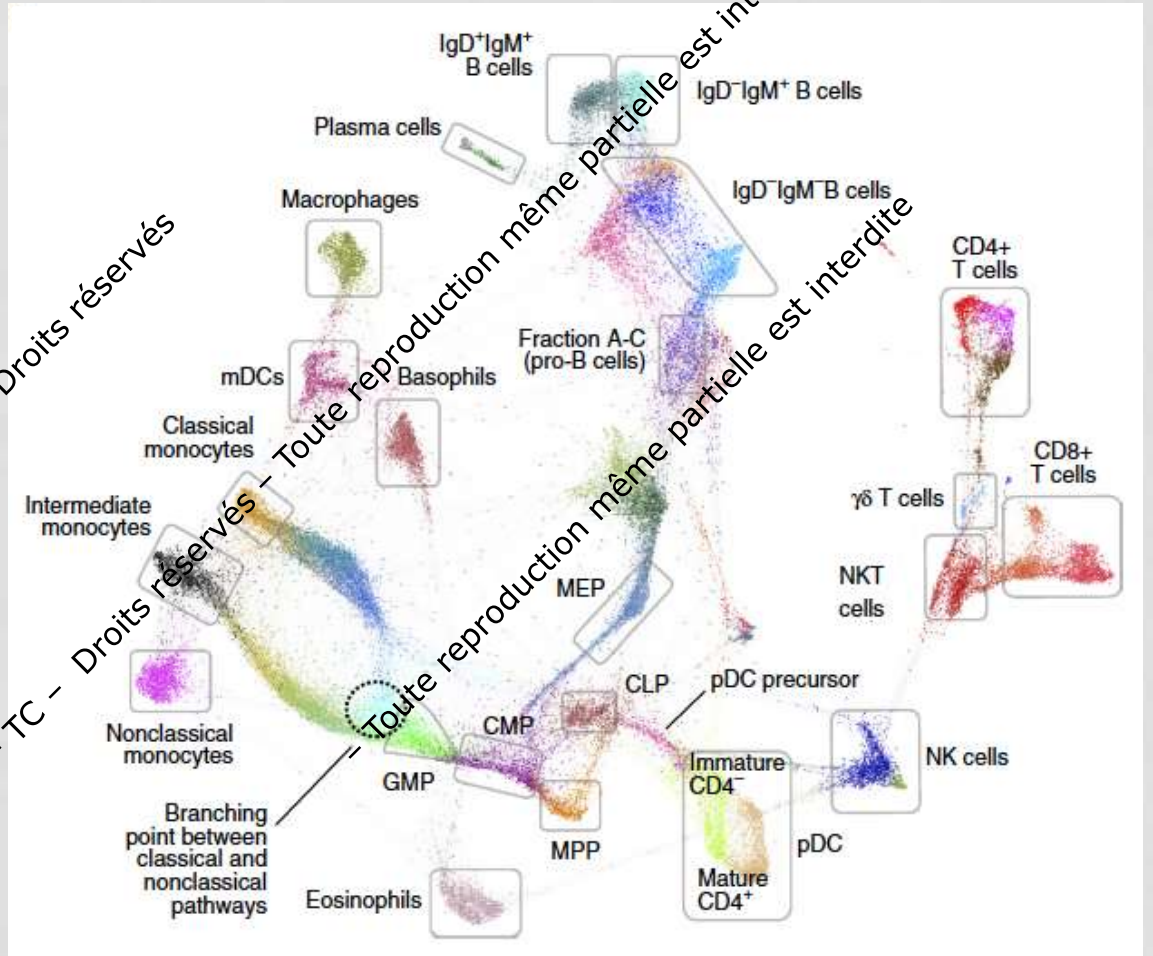
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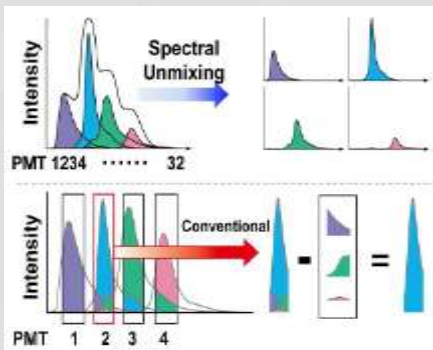
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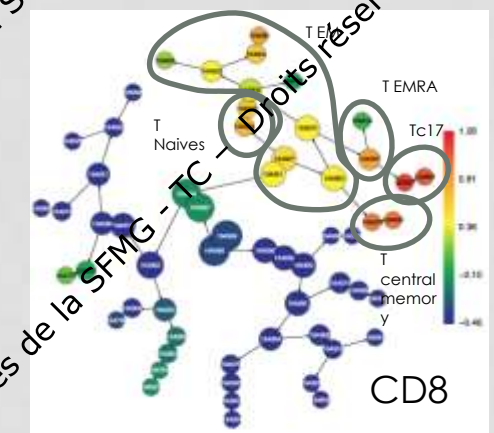
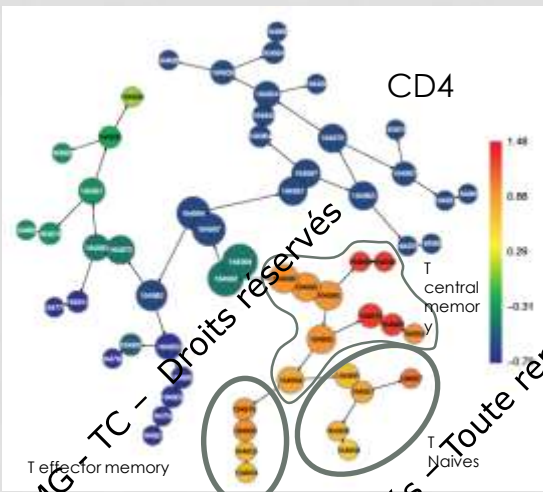
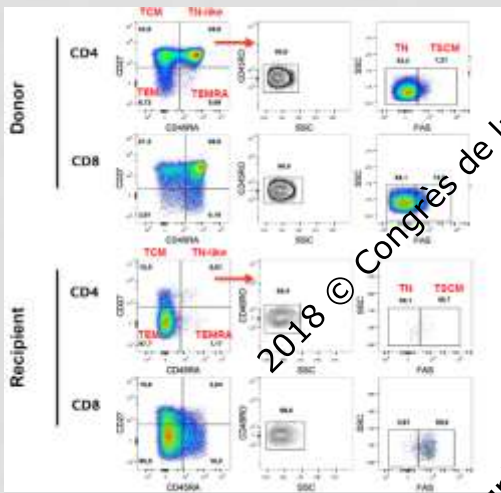


Stern, Front Immunol, 2018
 Samusik N et al.
 Nature Methods 13, 493–496 (2016)

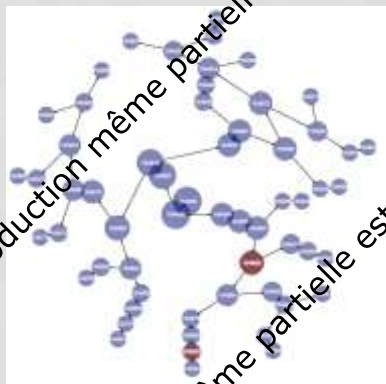




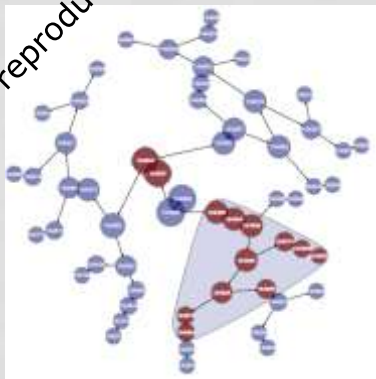
spectral flow cytometry



Predictive model



Descriptive model (FDR<1%)



GvHD Y/N



Hôpitaux Universitaires
SAINT-LOUIS
LARIBOISIÈRE
FERNAND-WIDAL



Institut Pasteur

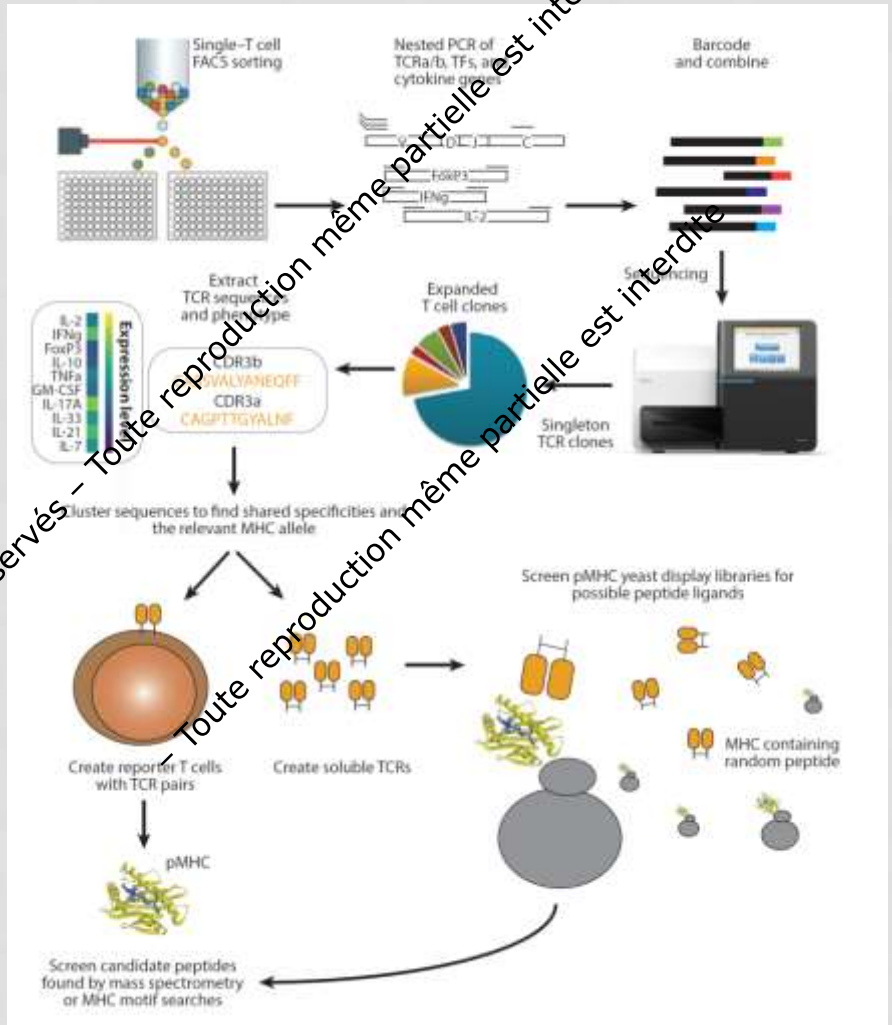


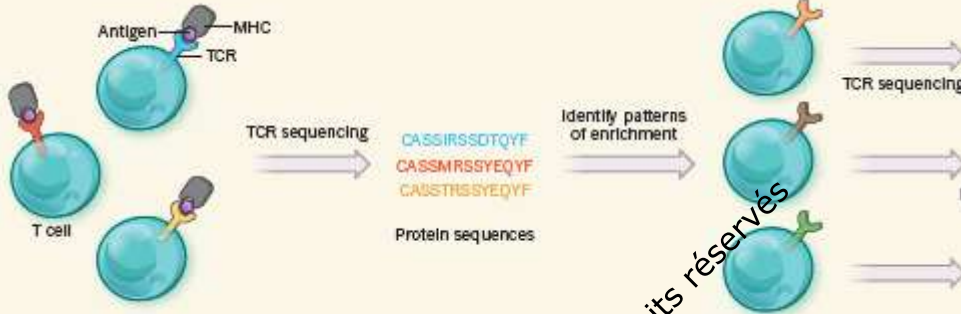
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ANNUAL
REVIEWS

Annual Review of Immunology
Rebooting Human Immunology

Mark M. Davis¹ and Petter Brodin²





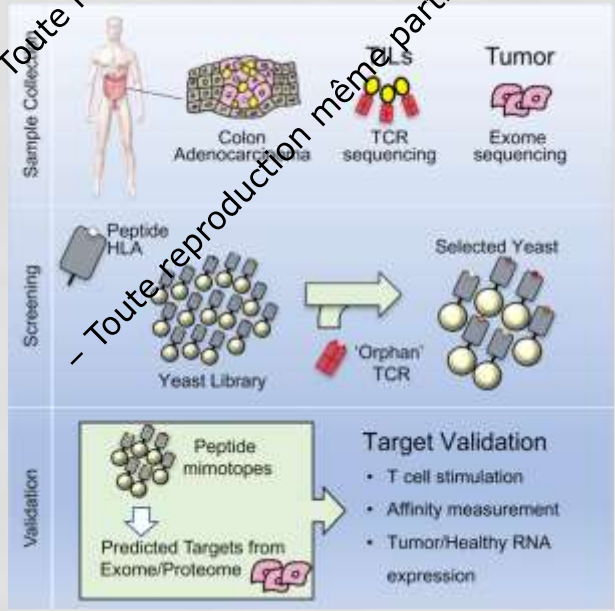
Predicted Ag-specific binding

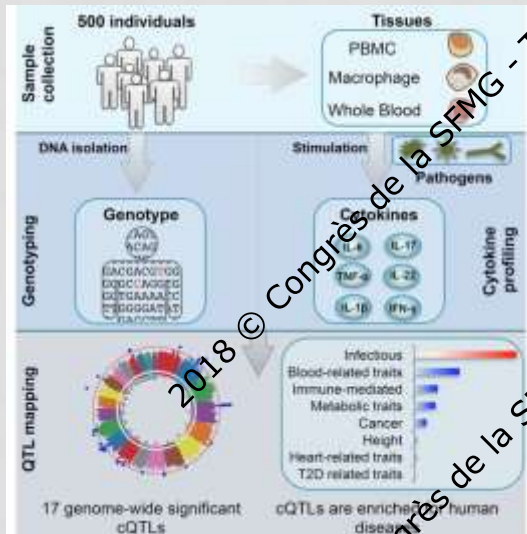
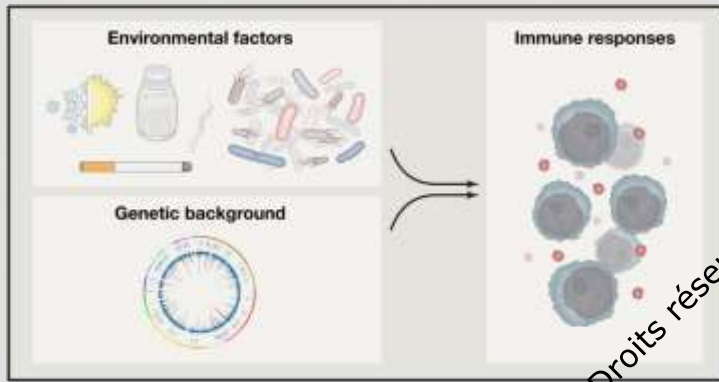


2017; 547:

- 36-38
- 89-93
- 94-98

Cell
 Article
 2018; 172: 549-63
Antigen Identification for Orphan T Cell Receptors Expressed on Tumor-Infiltrating Lymphocytes

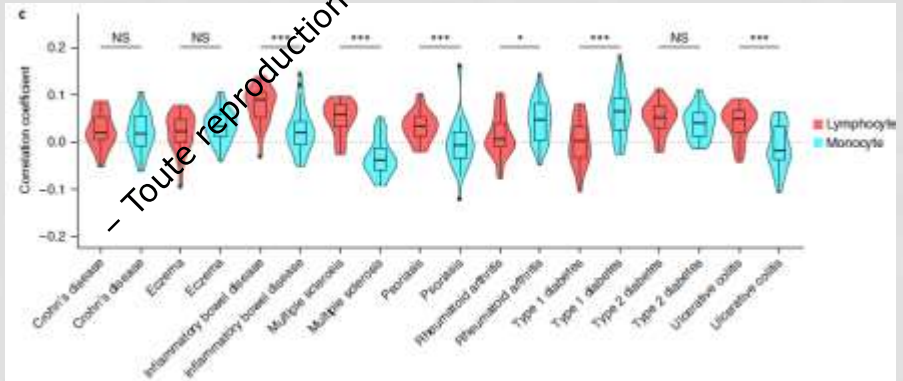


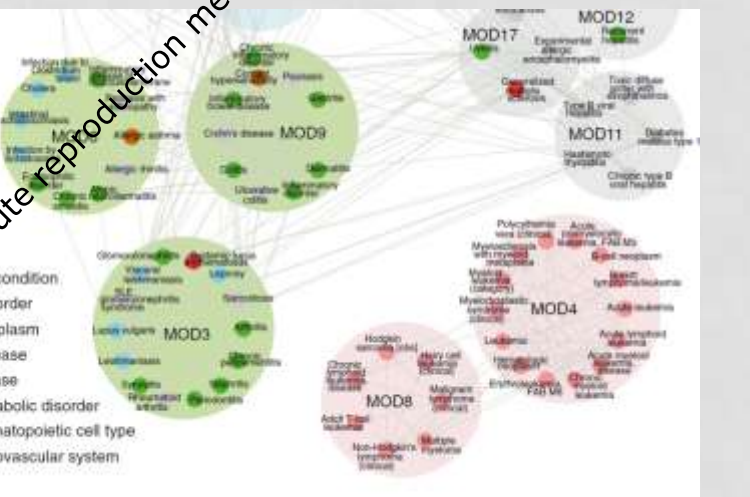
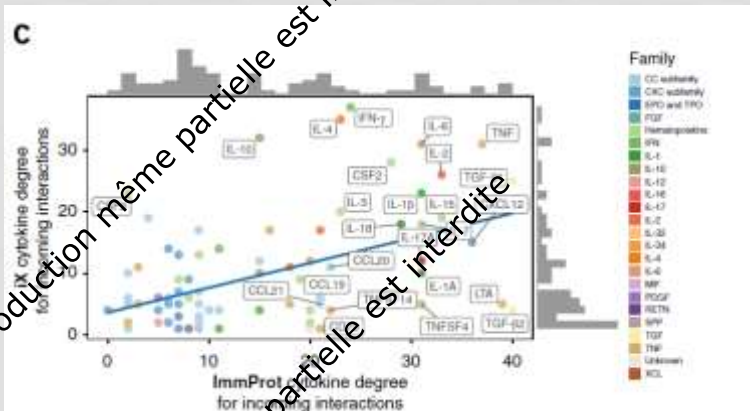
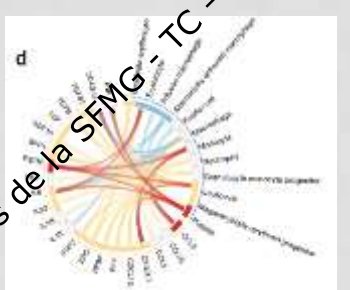
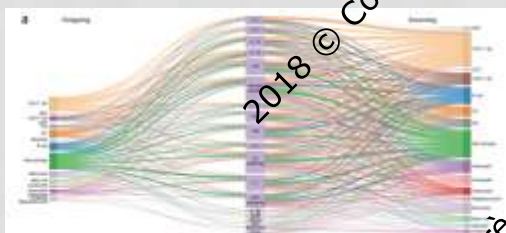
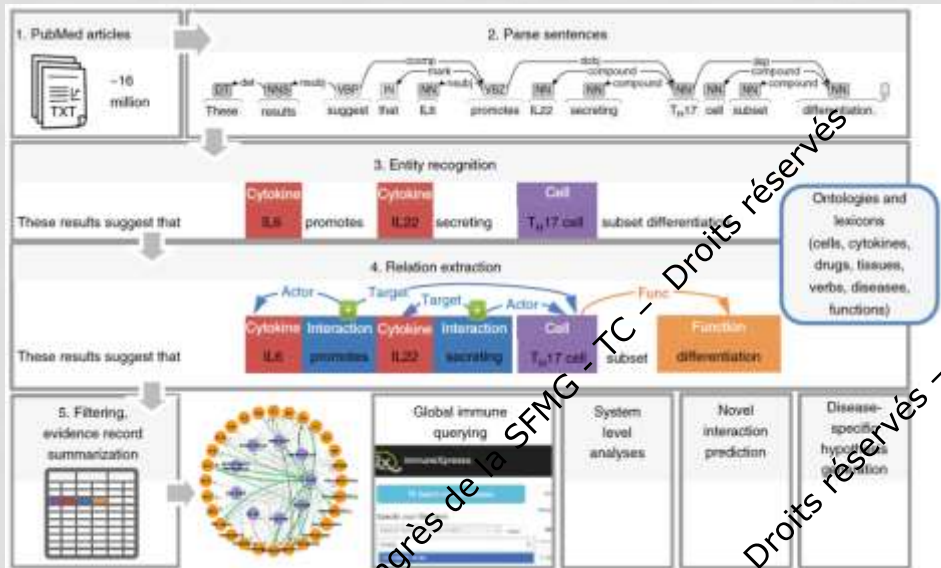


The Human Functional Genomics Project: Understanding Gene Regulation and the Generation of Diversity

Cell
 2016; 167: 1099-110
 1111-24
 1125-36

nature immunology
 2018; 19: 776-86





A Classical statistical association

Associate molecular variants with disease

Heterogeneity mask all but strongest effects

B Modern machine learning

Accurate predictions given many samples

Black box, high complexity, low sample size

C Experimental Cell Biology

Rapid mapping of biological mechanisms

Disconnected from patient data

D Biomedical text mining

Assimilation of data & mechanisms from literature

Most answers not in literature

Visible
Intelligence
Infrastructure

