L'inhibition des protéines BET : une thérapie épigénétique pour les lymphomes B de haut grade

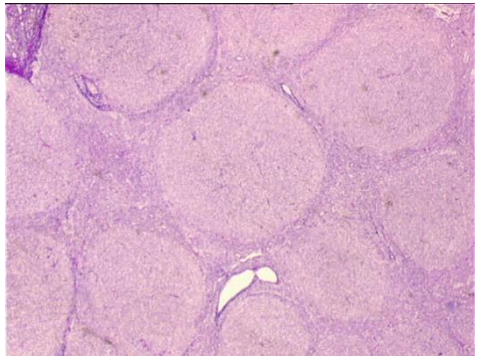
Dr Rémy Gressin, PH Hématologie Clinique, CHUGA

Dr Anouk EMADALI, Institut pour l'Avancée des Biosciences

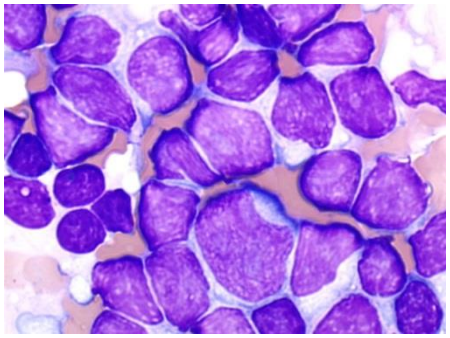
Pôle Recherche CHUGA

Génétique et Epigénétique des Cancers lymphoïdes > Epigénétique translationnelle

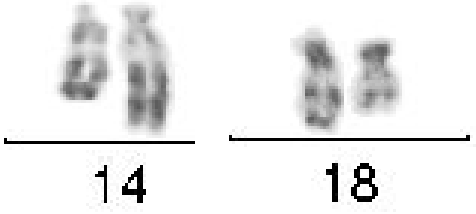
Biopsie - Analyse multidisciplinaire
Diagnostic d'entité



Histologie - IH

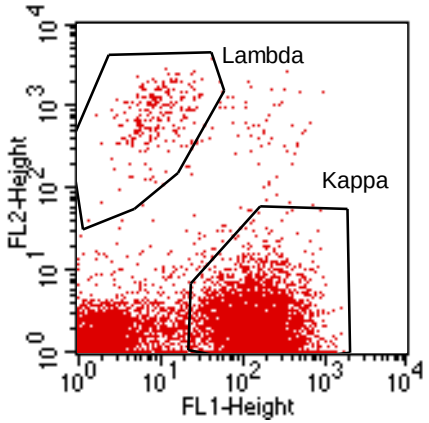


Cytologie



Cytogénétique
FISH

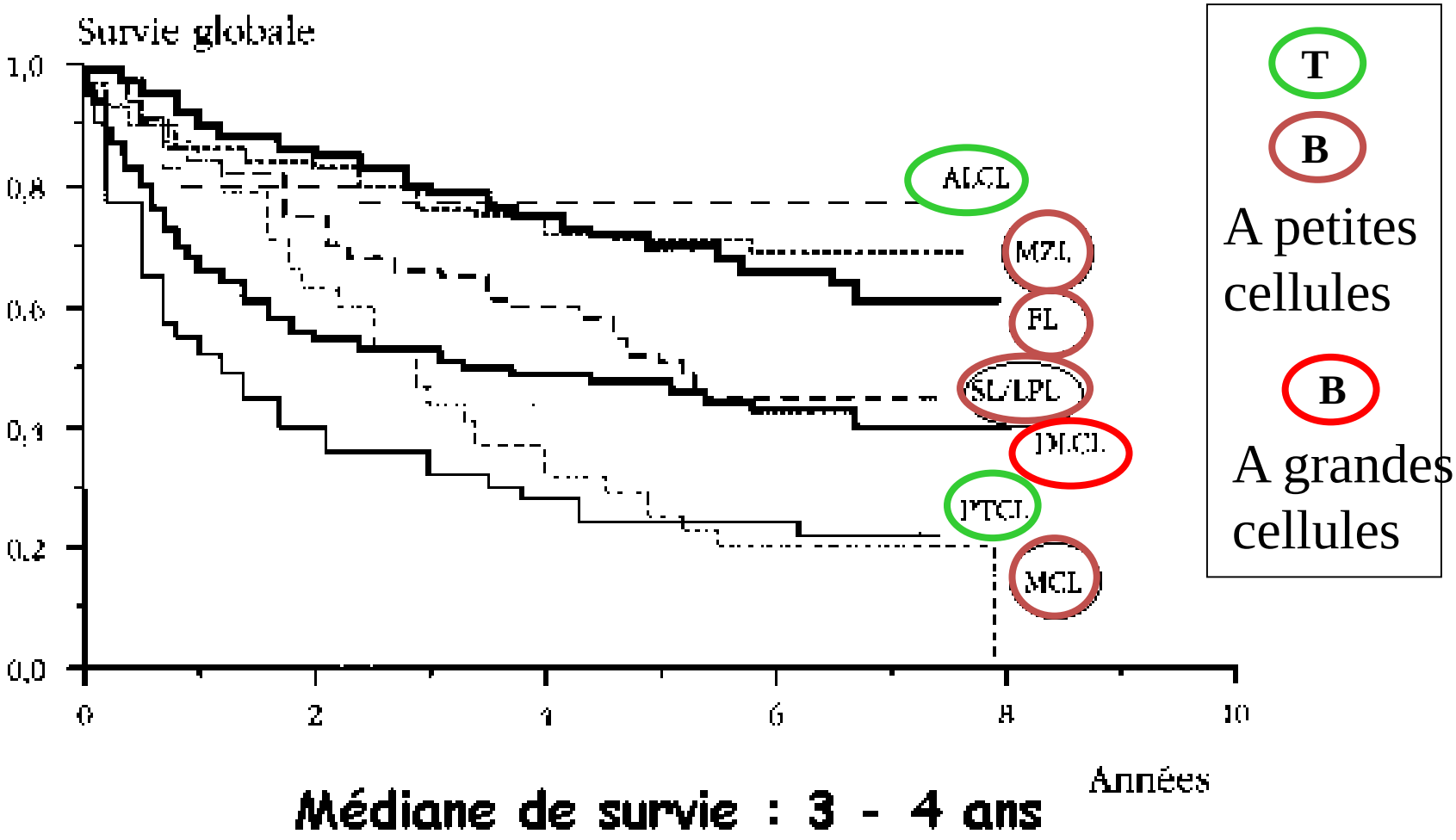
ENTITE



Immunophénotypage
CMF

Biologie moléculaire / PCR - NGS
réarrangement (ex BCL2/JH)

Valeur pronostique de l'entité

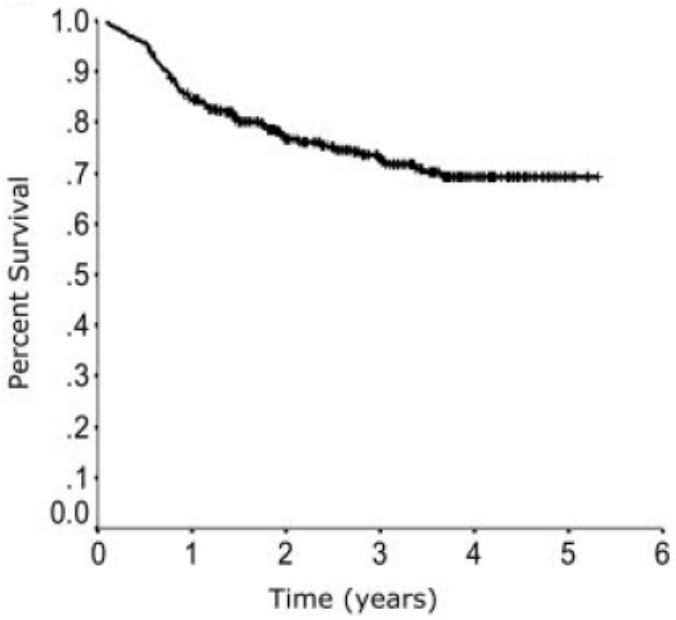


Médiane de survie : 3 - 4 ans

Survie des 1 254 malades inclus dans l'étude de validation de la Real classification en fonction des types histologiques.

Immuno chimiothérapie : le schéma R-CHOP

- **R**ituximab Mabthera ® :375 mg/m^2	IV	J1
- **C**yclophosphamide ENDOXAN® : 750 mg/m2	IV	J1
- **H**ydroxyAdriamycine DOXORUBICINE®: 50 mg/m2	IV	J1
- **O**NCOVIN® : 1.4 mg/m2	IV	J1
- **P**REDNISONE : 40 mg/m2	PO	J1-5



Guérisons 60%

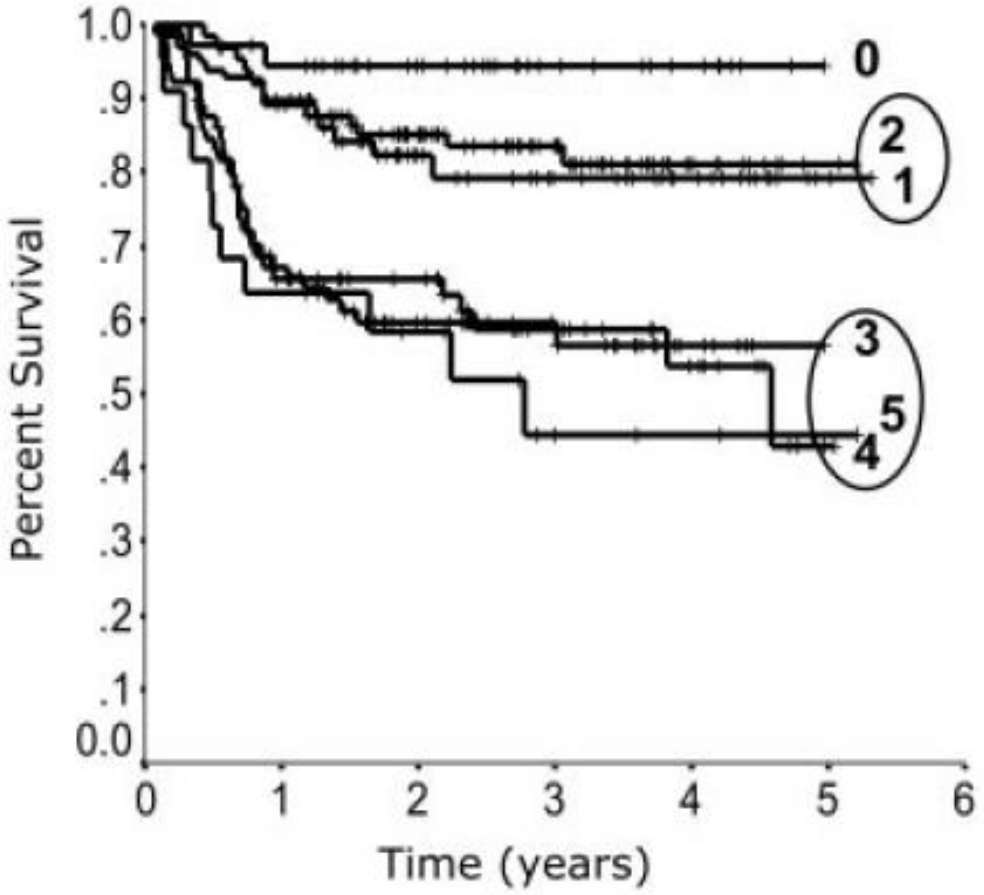
Rechutes et décès 40%

Sehn, Blood 2007

Index R-IPI
Rituximab International Prognostic Index

5 facteurs indépendants

- Age : < vs > 60 ans
- Stade I-II vs III-IV
- ECOG 0-1 vs 2-3 ou 4
- N site extra gg: <2 vs ≥2
- LDH : N vs >N



WHO classification 2008 → new 2016

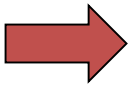
Diffuse large B-cell lymphoma.

Diffuse large B-cell lymphoma (DLBCL), NOS
- T-cell/histiocyte rich large B-cell lymphoma (T/HRBCL)
- EBV+ DLBCL of the "elderly"

DLBCL with a predominant extranodal location
- Primary mediastinal (thymic) large B cell lymphoma (PMBL)
- Intravascular large B-cell lymphoma (IVLBCL)
- Primary cutaneous DLBCL, leg type (PCLBCL, leg type)
- Primary DLBCL of CNS
- Lymphomatoid granulomatosis

Large-cell lymphomas of terminally differentiated B-cells
- ALK positive large B-cell lymphoma
- Plasmablastic lymphoma (PBL)
- Primary effusion lymphoma (PEL)
- DLBCL associated with chronic inflammation

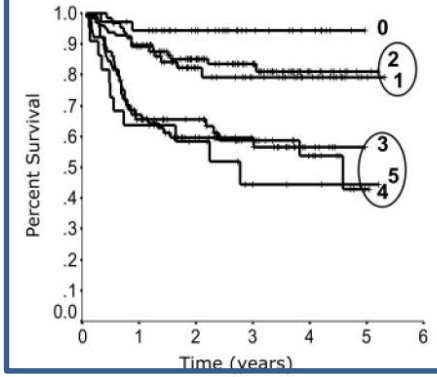
B-cell neoplasms with features intermediated between DLBCL and other lymphoid tumours
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse and
  - Large B-cell lymphoma and Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse and
  - Large B-cell lymphoma and classical Hodgkin lymphoma



- *Large B-cell lymphoma with IRF4 rearrangement**
- Primary cutaneous follicle center lymphoma
- Mantle cell lymphoma
  - In situ mantle cell neoplasia*
- Diffuse large B-cell lymphoma (DLBCL), NOS
  - Germinal center B-cell type*
  - Activated B-cell type*
- T-cell/histiocyte-rich large B-cell lymphoma
- Primary DLBCL of the central nervous system (CNS)
- Primary cutaneous DLBCL, leg type
- EBV^+ DLBCL, NOS*
- *EBV^+ mucocutaneous ulcer**
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK^+ large B-cell lymphoma
- Plasmablastic lymphoma
- Primary effusion lymphoma
- *$HHV8^+$ DLBCL, NOS**
- Burkitt lymphoma
- *Burkitt-like lymphoma with 11q aberration**
- High-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements*
- High-grade B-cell lymphoma, NOS*
- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

RCHOP la référence - Facteurs Pronostiques

Index R-IPI



5 facteurs indépendants
- Age : < vs > 60 ans
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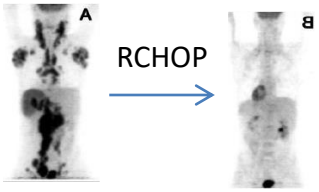
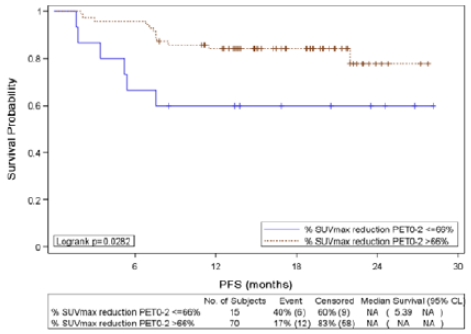
Sehn, Blood 2007

TEP interim



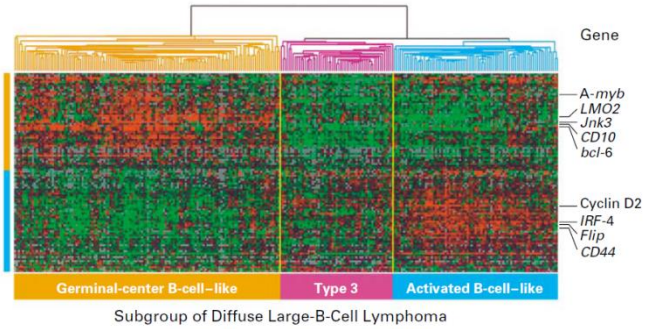
Calcul deltaSUV



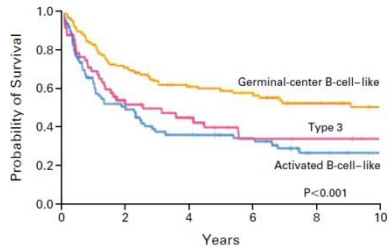
Casasnovas Blood 2012

COO

GEP

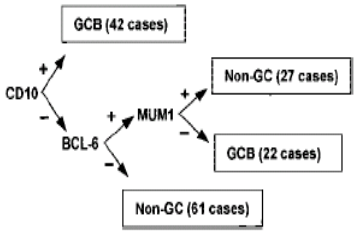


Subgroup of Diffuse Large-B-Cell Lymphoma

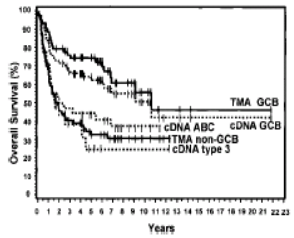


Rosenwald, NEJM 2002

IH



. Decision tree for immunoperoxidase TMA classification of DLBCL

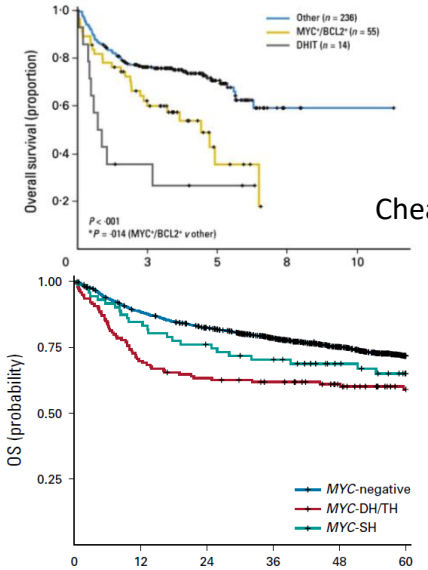


Non reproductible:
Corrélation NonGC 80%
GC 95%

Hans CP, Neoplasia 2004

Doubles/Triples Hit

Cmyc et Bcl2, Bcl6: 5-10% des DLBCL



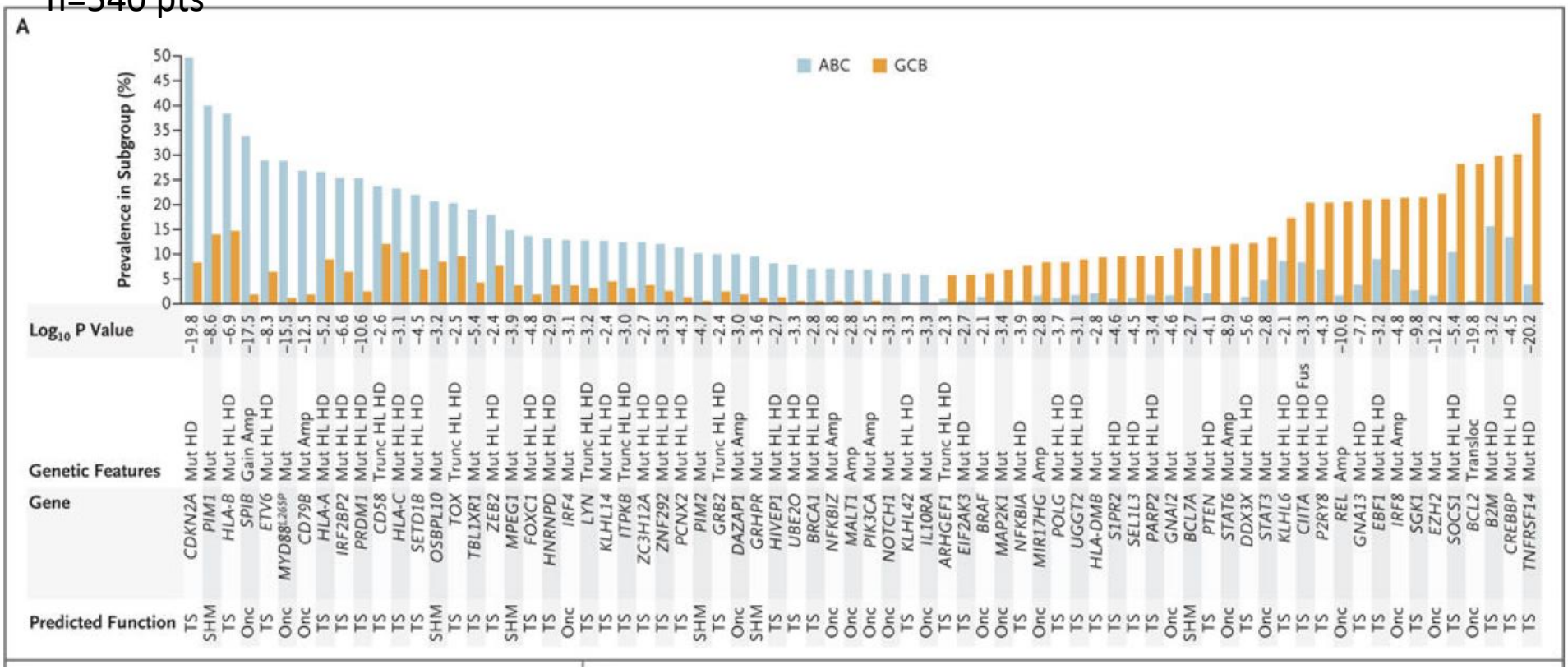
Cheah CY, BJH 2014

Gene partenaire de myc- IGh, K, L

Rosenwald A, JCO 2019

Apport profils mutationnels
NGS: Séquençage haut débit

n=540 pts



Schmitz & Staudt, NEJM 2018

Combinatoire : DNAseq (WES)+RNAseq (exomes)+SV+ CopyN

n=540 pts

Classés: 44,8%

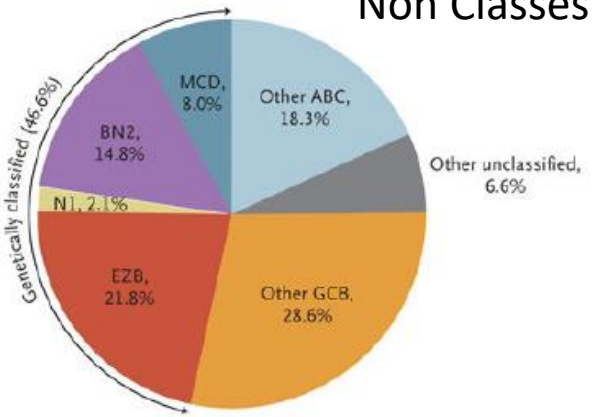
Non Classés: 55.2%

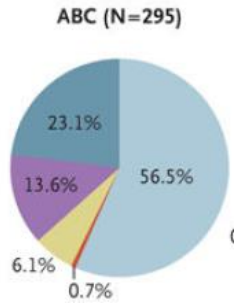
MCD: MYD88L265P + CD79B muté

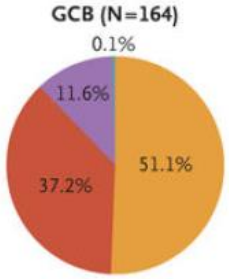
BN2: BCL6 fusion + Notch2 muté

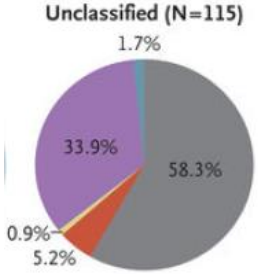
N1: Notch 1 muté

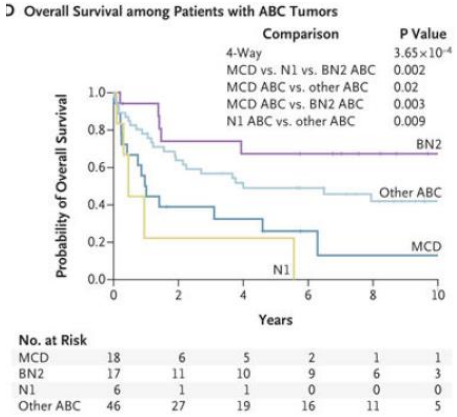
EZB: EZH2 muté + BCL2 transloqué

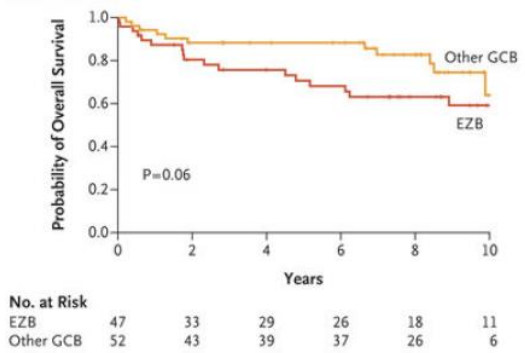






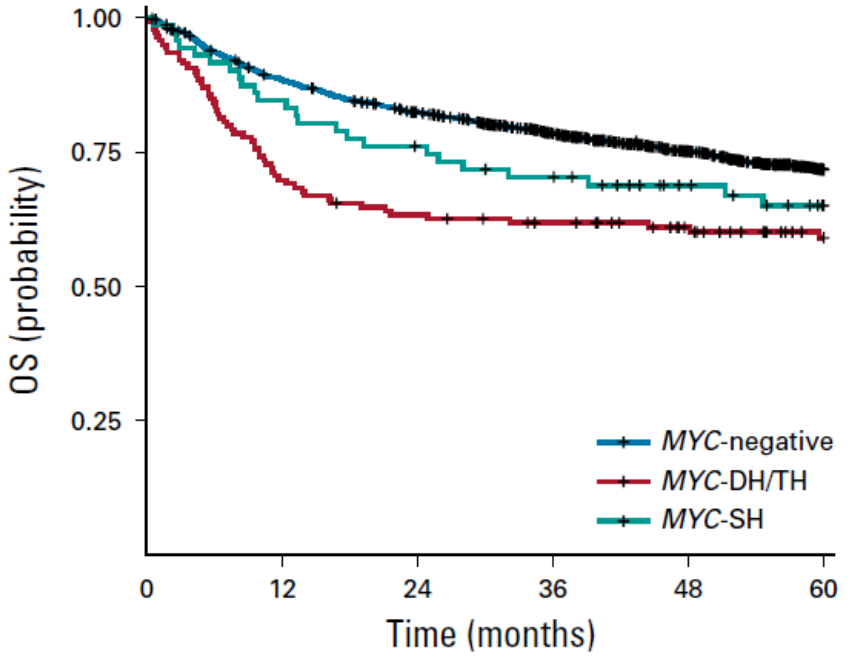






Schmitz & Staudt, NEJM 2018

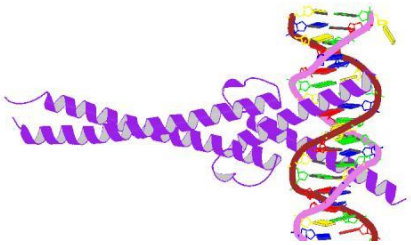
Double/Triple Hit – MYC,BCL2,BCL6

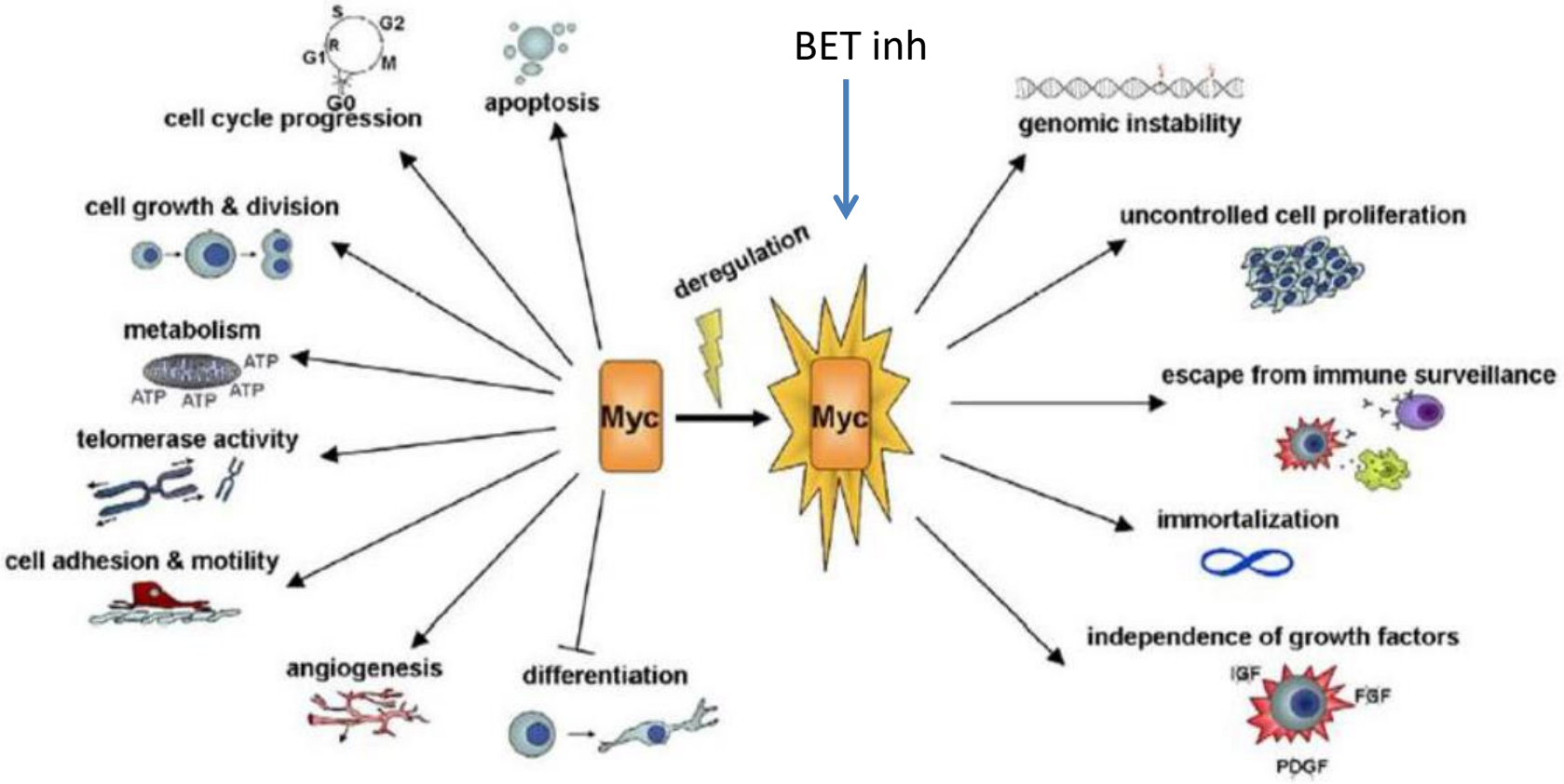


No. at risk:						
MYC-negative	2,119	1,858	1,716	1,556	1,353	1,106
MYC-DH/TH	139	97	87	81	69	54
MYC-SH	72	60	53	48	38	29

Rosenwald, JCO 2019

MYC

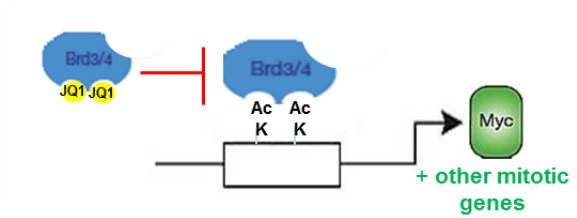


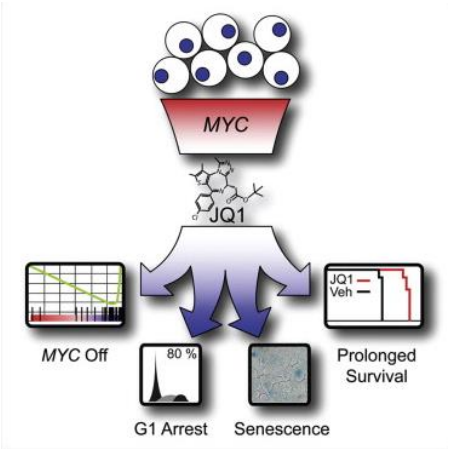


Vita & Henriksson, 2006

BET inhibition in hematological malignancies

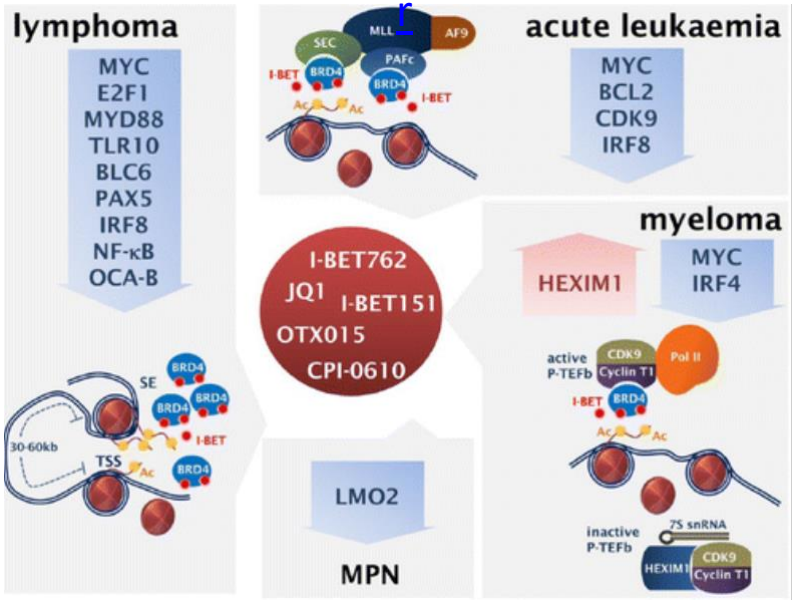
Targets: **1) MYC**





Filippakopoulos et al, Nature, 2010
Zuber et al, Nature, 2011,
Delmore et al, Cell, 2011
Mertz et al, PNAS, 2011
Ott et al, Blood, 2012

2) Master regulators of germinal center and lymphomagenesis

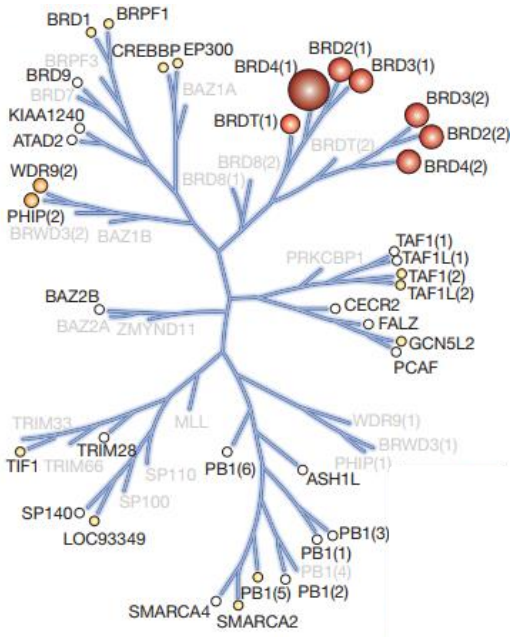


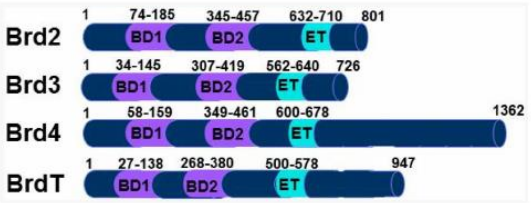
Chapuy, Cancer Cell, 2013

Loven, Cell, 2013

Super-enhancers oncogenic transcription : selectivity of anti-tumor effects

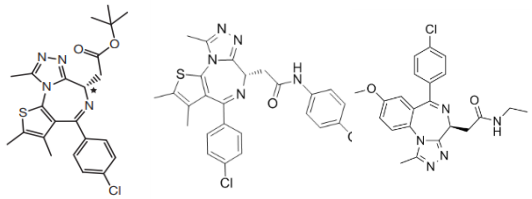
BET inhibition : Drug development





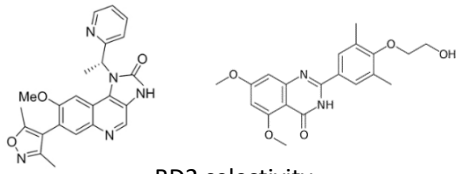
Diazepines

JQ1 **OTX015** **iBET-762**

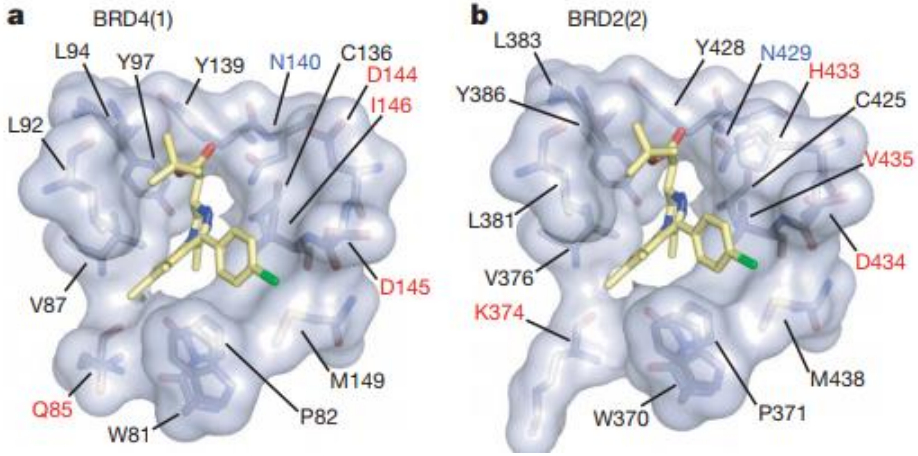


Quinolines/quinazolones

iBET-151 **RVX208**



BD2 selectivity



Filippakopoulos, Nature, 2010

BET inhibition : Early phase clinical trials

Drug	Phase	ClinicalTrials.gov identifier	Status	Lymphoma patients	Responses in lymphoma patients	Reference
AZD5153	1	NCT03205176	Recruiting	Yes	No data reported	No data reported
BAY 1238097	1	NCT02369029	Terminated	No[a]	–	Reported [62]
BI 894999	1	NCT02516553	Recruiting	No data reported	No data reported	Abstract [55]
Birabresib (OTX015/MK-8628)	1	NCT01713582	Completed	33 (67% DLBCL)	2 CR (DLBCL), 1 PR (DLBCL), 6 minor responses	Reported [51,60]
BMS-986158	1/2	NCT02419417 (single agent and in combination with nivolumab)	Recruiting	No data reported	No data reported	Abstract [56]
CC-90010	1	NCT03220347	Recruiting	Yes (1 lymphoma)	–	Abstract [66]
CPI-0610	1	NCT01949883	Active, not recruiting	64 (56% DLBCL)	2 CR (ABC DLBCL, TCHR DLBCL), 3 PR (2 ABC DLBCL, 1 FL), 5 SD	Abstract [52]
FT-1101	1	NCT02543879	Recruiting	No data reported	No data reported	No data reported
GS-5829	1	NCT02392611	Completed	No data reported	No data reported	No data reported
INCB054329	1/2	NCT02431260	Completed	Yes [4]	No data reported	Abstract [57]
INCB057643	1/2	NCT02711137 (single agent and in combination with standard-of-care)	Active, not recruiting	Yes (3 FL)	1 CR, 2 SD	Abstract [53]
Mivebresib (ABBV-075)	1	NCT02391480 (single agent and in combination with venetoclax)	Active, not recruiting	No data reported	No data reported	Abstract [67,68]
Molibresib (GSK525762/ I-BET762)	1	NCT01943851	Recruiting	Yes (19 B-cell, 8 T-cell)	1 CR (DLBCL), 4 PR (1 DLBCL, 3 CTCL)	Abstract [54]
PLX51107	1/2	NCT02683395	Terminated (Business Decision)	Yes	No data reported	Abstract [58]
RG6146 (RO6870810/ TEN-010)	1	NCT01987362	Completed	Yes (19 DLBCL)	2 PR	Abstract [69]
RG6146 (RO6870810/ TEN-010)	1	NCT03255096 (combination with venetoclax with and without rituximab)	Recruiting	Yes	No data reported	No data reported

ABC, activated B-cell subtype; CR, complete response; CTCL, cutaneous T-cell lymphomas; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; PR, partial response; SD, stable disease; TCRH, T-cell/histocyte-rich.
[a]Enrollment planned for lymphoma patients but early closure because of toxicity.

Single agent – Phase I/II
Dose escalation studies

Berthon, Lancet Haematology, 2016 - AML
Amorim, Lancet Haematology, 2016 - DLBCL, MM

Severe side effects :

thrombocytopenia, gastrointestinal events, fatigue

But, evidence of clinical activity :

- **Complete responses**
- **Partial responses**

Emerging class of anti-cancer targets, but rational is lagging…

Identification of an iBET-sensitive gene regulatory circuit in high grade B-cell lymphoma

NUCLEAR PROTEOME
Model : high-risk B-cell lymphoma
B593 « double hit » DLBCL cell line

B593 cell line

NUCLEI PREPARATION

B593 nuclei

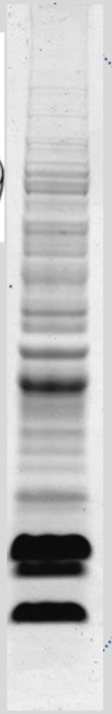
ACID EXTRACTION

Nucleic acid-soluble (NAS) fraction

1D SDS-PAGE

TRYPSIN DIGESTION

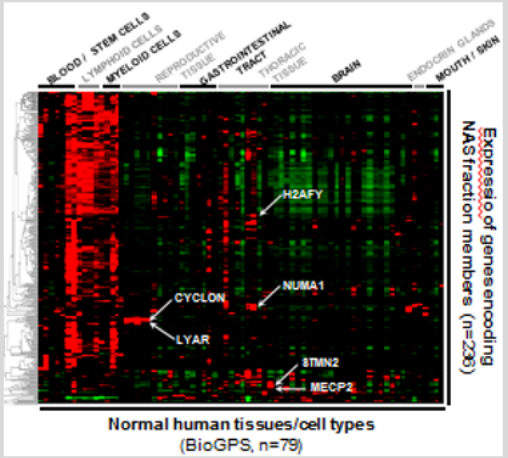
LC/MS-MS

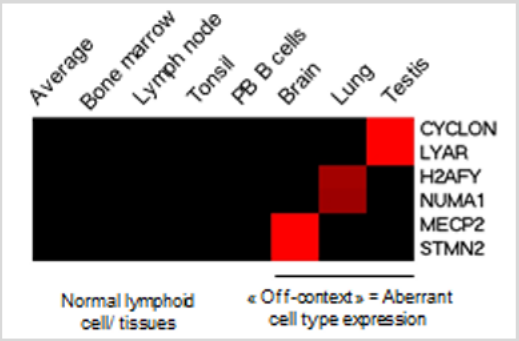


B593 NAS fraction 236 proteins

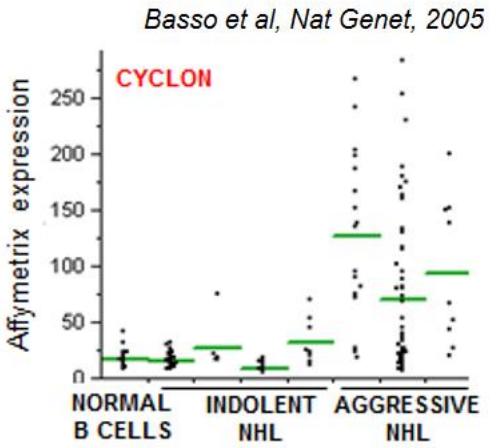
Reference cancer sub-proteome enriched in nucleic acid binding and associated proteins

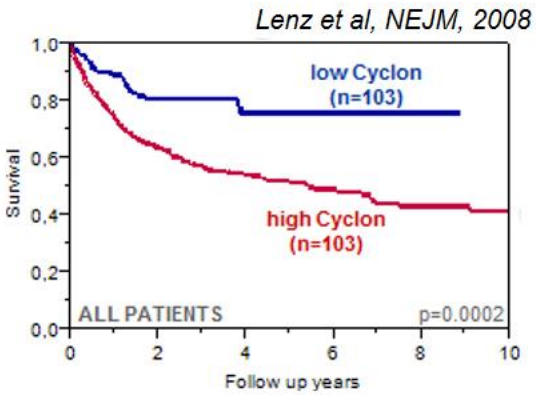
NORMAL TISSUE GENE EXPRESSION PROFILE
Meta-analysis of public expression database

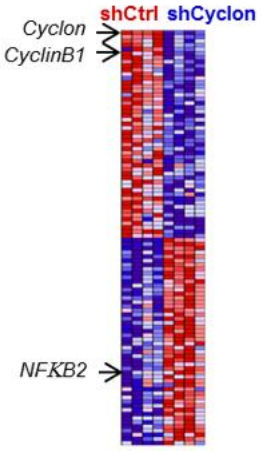


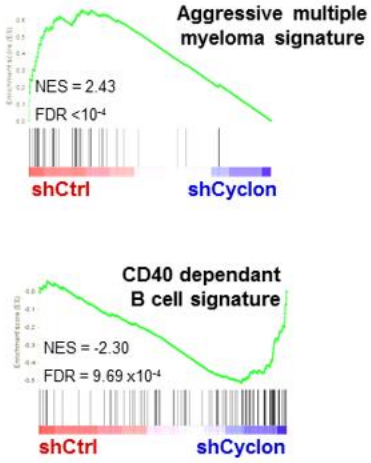


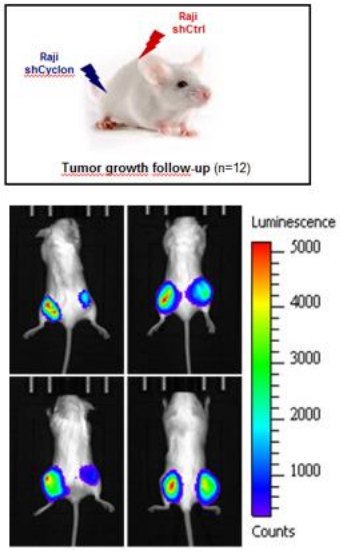
CYCLON is an autonomous tumor growth driver associated with disease aggressivity

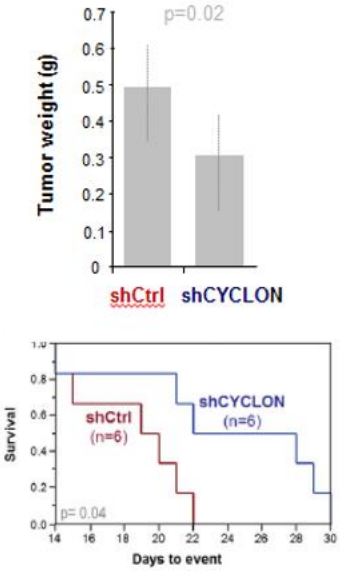




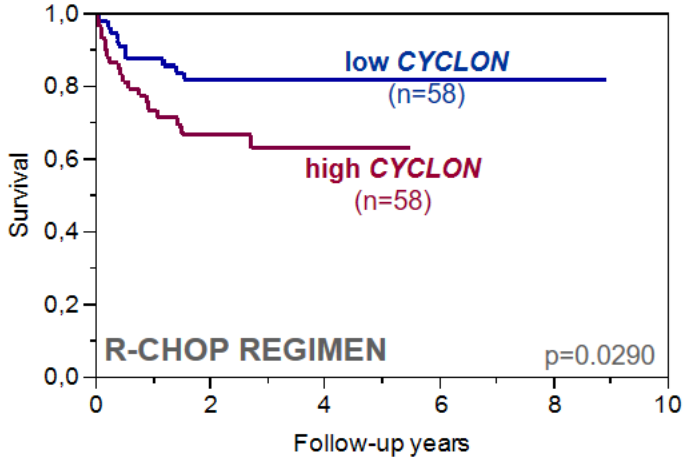


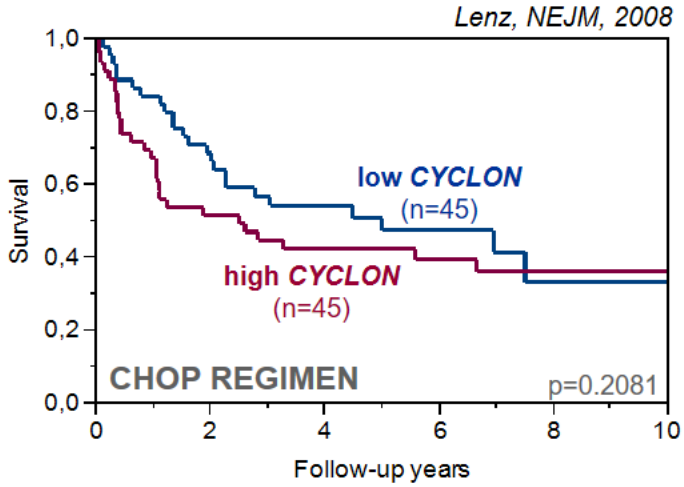


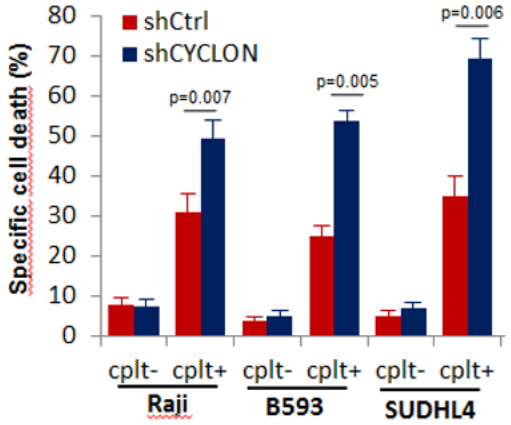


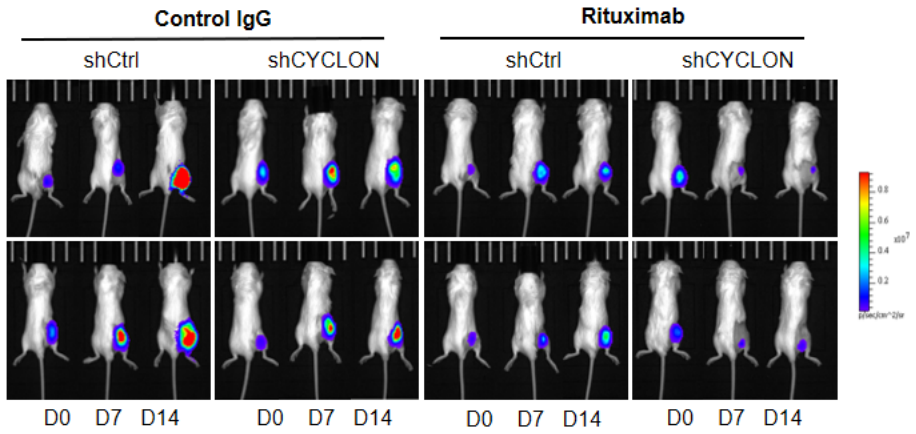


CYCLON is involved in resistance to anti-CD20 immunotherapy (Rituximab)

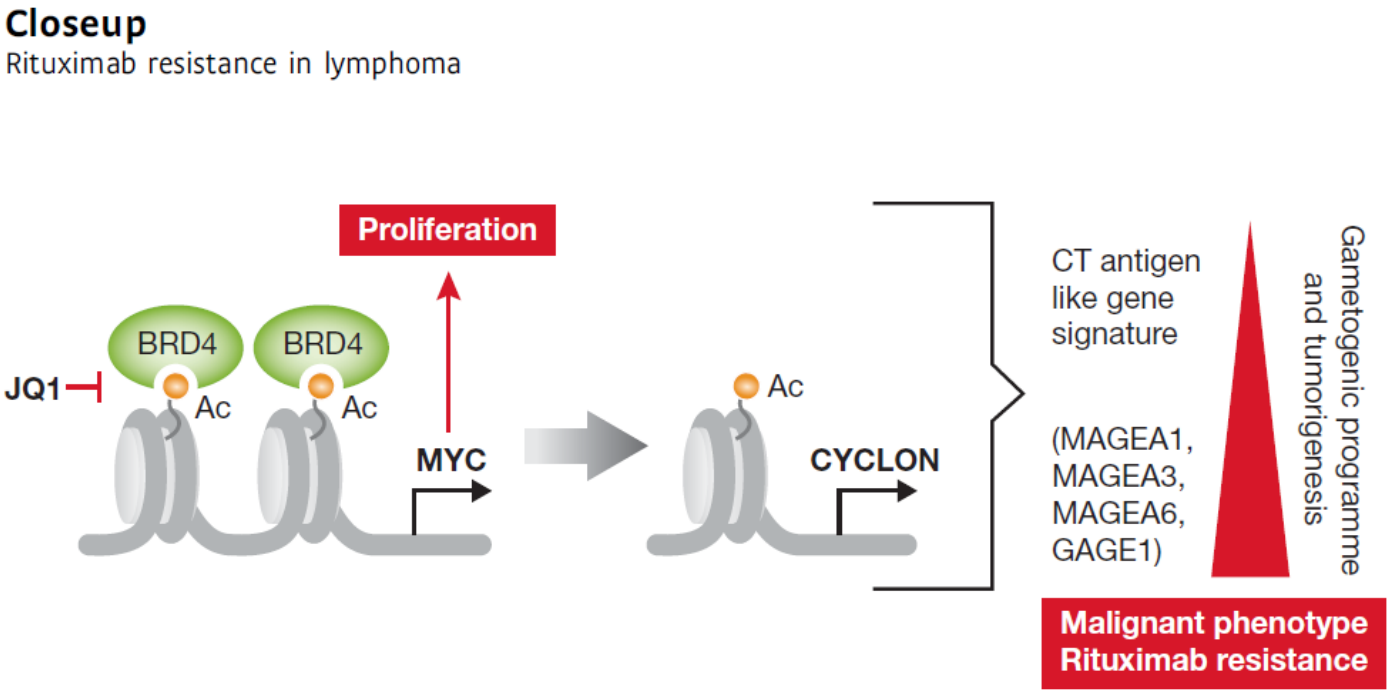








Identification of an iBET-sensitive gene regulatory circuit in high grade B-cell lymphoma

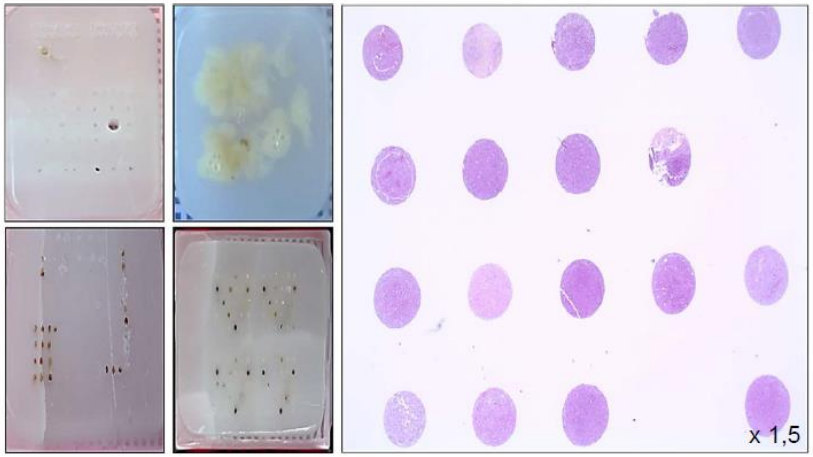


Emadali, EMBO Mol Med, 2013
Knapp, EMBO Mol Med, 2013
Patent PCT/EP2013/050336

Clinical evaluation of CYCLON as a predictive biomarker of anti-CD20 response in DLBCL

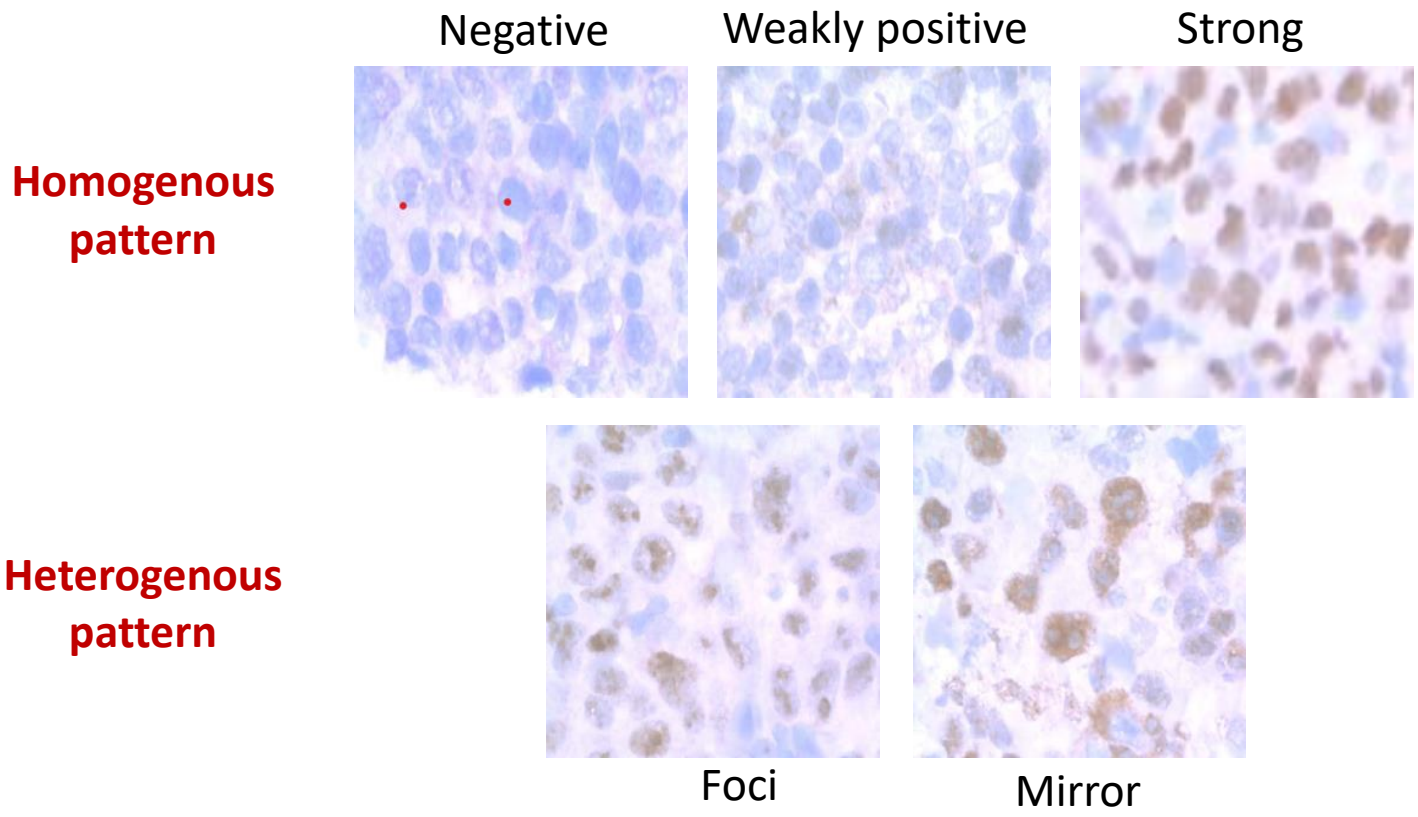
DLBCL retrospective cohort (>100 patients CHUGA patients)

- R-CHOP treated
- Full clinical annotations
- Tissue microarray



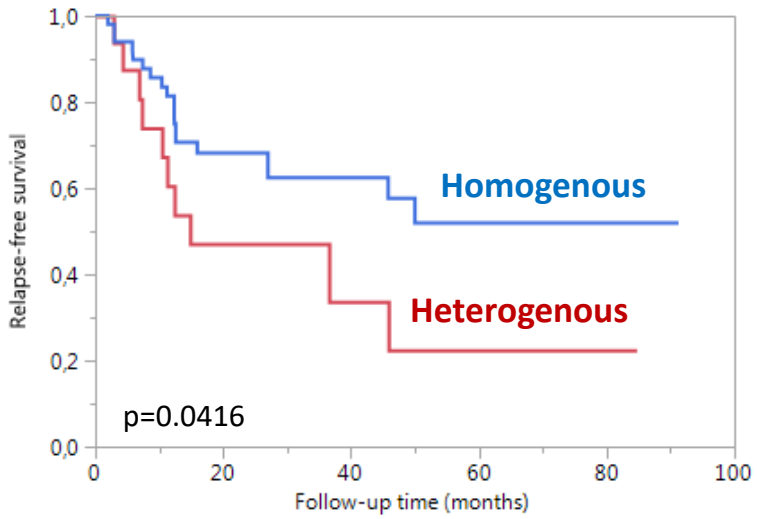
Hervé Sartelet - Antonin Bouroumeau
Rémy Gressin - Lucile Bussot

Clinical evaluation of CYCLON as a predictive biomarker of anti-CD20 response in DLBCL



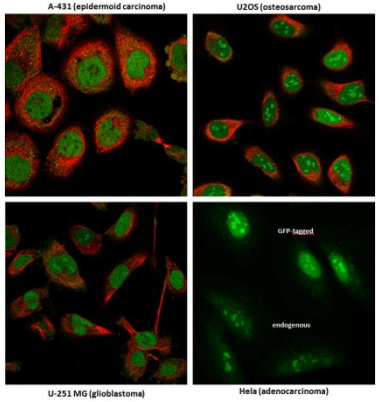
Hervé Sartelet - Antonin Bouroumeau

CYCLON subcellular localization pattern is associated with relapse-free survival



Variables	Type of variable	Survival criteria	Multivariate cox model		
			p-value	HR	95% CI (HR)
IPI score	Categorical	PFS	0.044	3.2	1.03-9.94
Staining pattern	Categorical	PFS	0.02	7.53	1.36-41.49

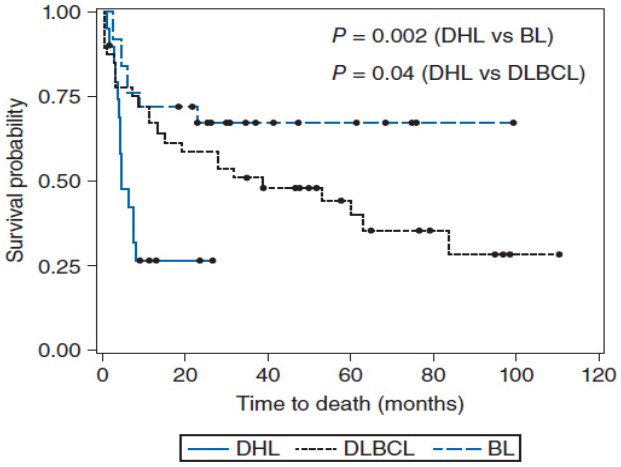
- Functional characterization of CYCLON nuclear substructures



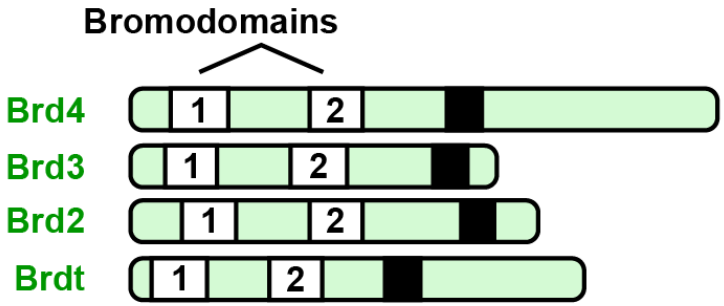
- Correlation with clinical, biological and genetic features to reveal further associations

Hervé Sartelet - Antonin Bouroumeau
Rémy Gressin - Lucile Bussot
Thierry Bonnefoix
Mary Callanan (CHU Dijon)

Function and inhibition of BET in double hit DLBCL



Lack of selectivity : 1 inhibitor, 8 BDs



Understand the contribution of each BET BD in lymphomas

Genetics
RNA-seq ATAC-seq
Proteomics

BD selective BET inhibitors in combination with other therapeutic agents

RVX208, iBET762, iBET26 (GSK)
Developed with YS Wong (DPM, Grenoble)

Jérôme Govin
Thèse Loris Delrieu (2019-2022)

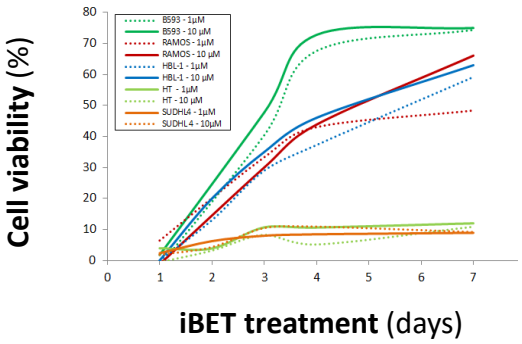
financé par
IDEX Université Grenoble Alpes

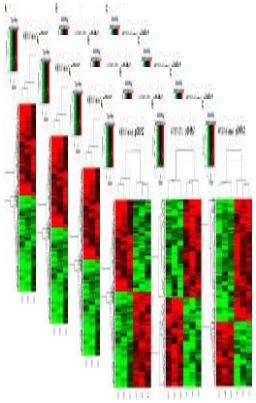
Resistance to BET inhibition in DLBCL

Predictive statistical modeling for personalized identification of druggable resistance factors

Gene expression profiling of DLBCL primary cells upon BET inhibition

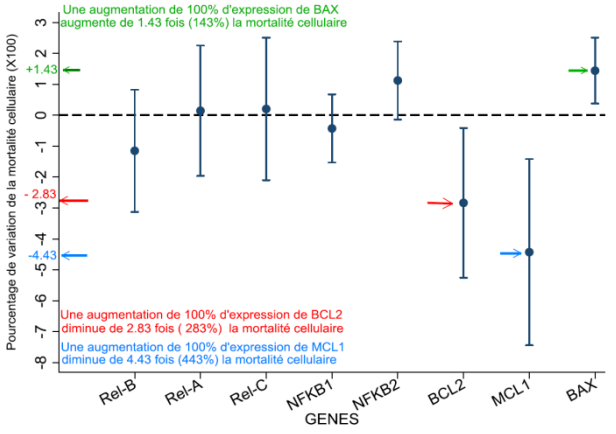
Cell viability and proliferation
RNA-seq





Identification of iBET target genes involved in therapeutic resistance

Generalized linear mixed models (accounting individual variability)



Elasticity : expected variation of gene expression according to cell death upon iBET treatment

Thierry Bonnefoix
Stage Master1 Sami El Mimouni
Rémy Gressin

Projet présélectionné : Appel d'offre d'interne CHUGA 2019
Volet Recherche innovante

Acknowledgements

Translational Epigenetics team (IAB)
Dr Jérôme Govin

Dr Thierry Bonnefoix
Sieme Hamaidia
Patricia Betton-Fraisse
Loris Delrieu
Sami El Mimouni

Dr Thierry Gauthier
Dr Camille Sayou
Marie Arlotto
Julie Marais
Sarah El Kennani
Kaiyao Wei

Collaborations
Mary Callanan (CHU-Dijon)
Yung-Sing Wong (DPM-UGA)
Laurent Genestier (CRCL)

Signaling through Chromatin Department
Dr Saadi Khochbin

IAB Platforms
Epimed: Dr Sophie Rousseaux, Florent Chuffart

Flow cytometry: Mylène Pezet

Hématologie Clinique
Dr Rémy Gressin

Lucile Bussot
Pr Sophie Park - Pr Jean-Yves Cahn

Anatomie et Cytologie pathologiques
Pr Hervé Sartelet - Antonin Bouroumeau

Hématologie, Onco-Génétique et Immunologie
Dr Christine Lefebvre

Dr Marie-Christine Jacob
Dr Tatiana Raskovalova
Dr Sylvain Carras