Understanding the pathogenesis of T Cell Lymphomas: implications on future treatments

Advances in Malignant lymphomas:
The case of extranodal and T-cell lymphomas

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ORIGINAL REPORT

International Peripheral T-Cell and Natural Killer/T-Cell Lymphoma Study: Pathology Findings and Clinical Outcomes

International T-Cell Lymphoma Project

Table 1. Major Lymphoma Subtypes by Geographic Region

Subtype	%		
	North America	Europe	Asia
PTCL-NOS	34.4	34.3	22.4
Angioimmunoblastic	16.0	28.7	17.9
ALCL, ALK positive	16.0	6.4	3.2
ALCL, ALK negative	7.8	9.4	2.6
NKTCL	5.1	4.3	22.4
ATLL	2.0	1.0	25.0
Enteropathy-type	5.8	9.1	1.9
Hepatosplenic	3.0	2.3	0.2
Primary cutaneous ALCL	5.4	0.8	0.7
Subcutaneous panniculitis-like	1.3	0.5	1.3
Unclassifiable T-cell	2.3	3.3	2.4

Abbreviations: PTCL, peripheral T-cell lymphoma; NOS, not otherwise specified; ALCL, anaplastic large-cell lymphoma; NKTCL, natural killer/T-cell lymphoma.

T-Cell Lymphomas in South America and Europe

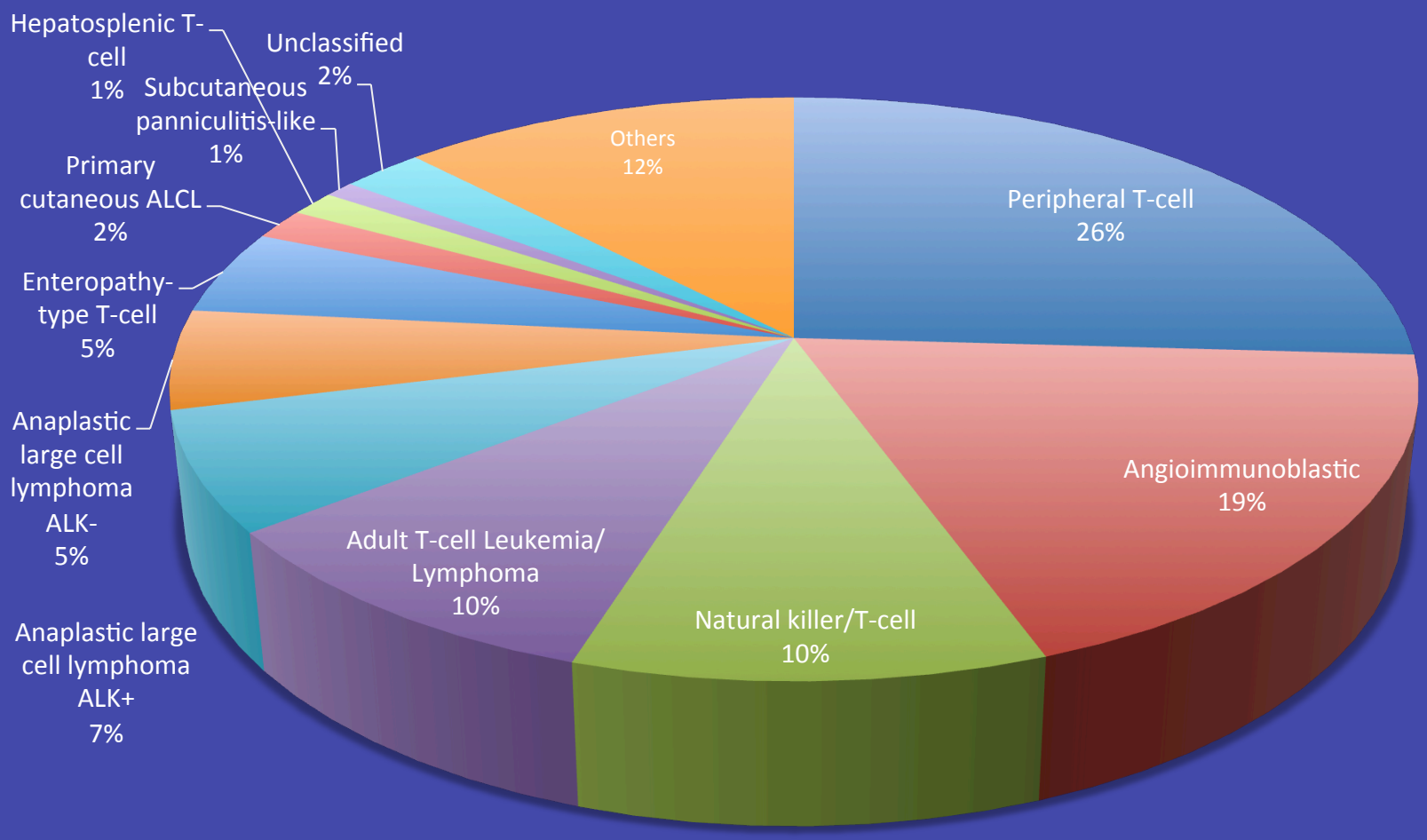
Table 2 - Histologic subtype distribution (%) according to reviewed histology of 737 cases registered in the T-cell project by geographic region

	Overall	Europe	USA	South America	Middle/ Far East
PTCL-NOS	38	40	42	42	26
AITL	17	20	21	8	15
ALCL, ALK^-	13	14	9	23	6
ALCL, ALK^+	7	6	8	8	4
NK/T nasal, nasal type, lymphoma/leukemia	13	6	9	13	31
Other histologies	12	14	11	6	18

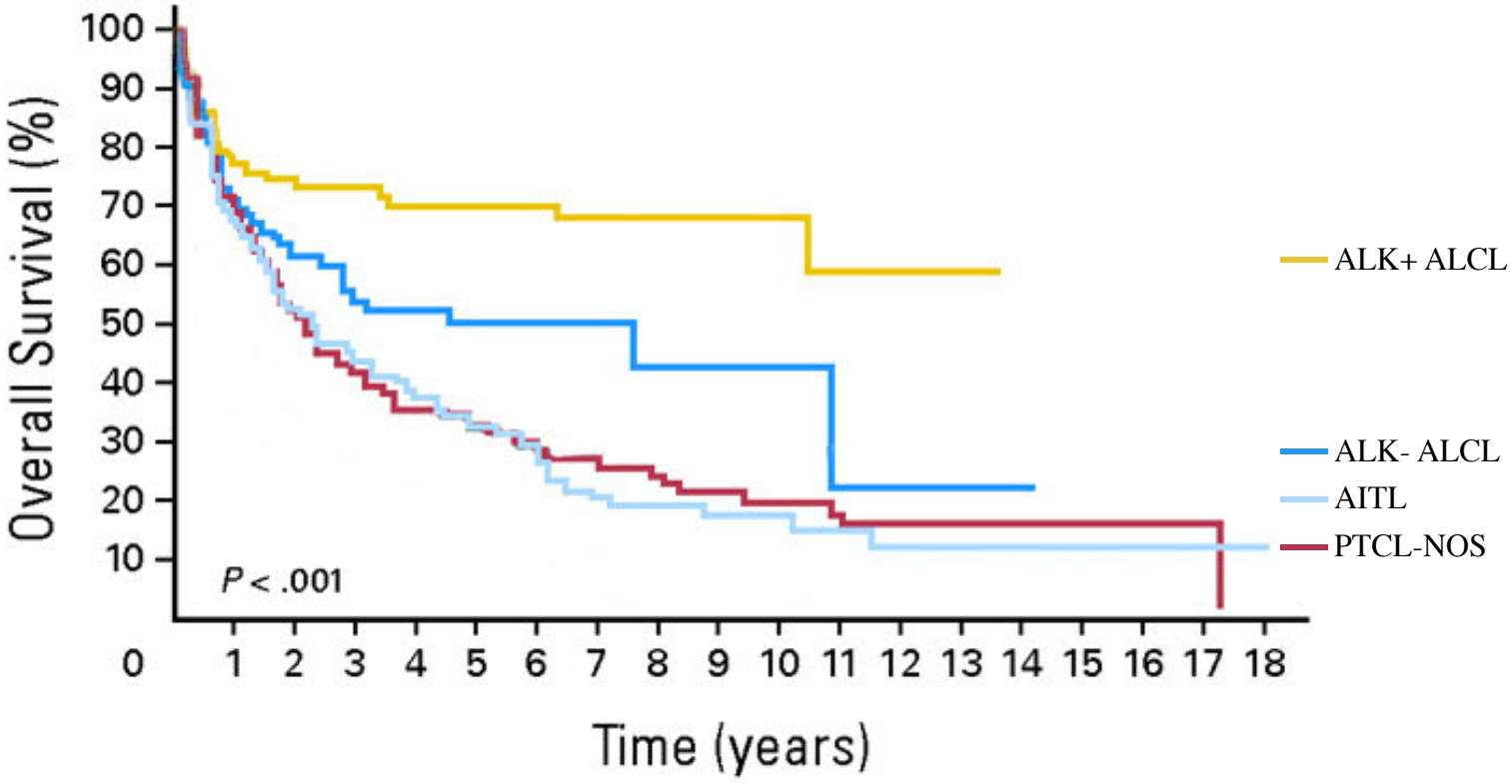
PTCL: Peripheral T-cell lymphomas; NOS: Not otherwise specified; AITL: Angioimmunoblastic T-cell lymphoma; ALCL: Anaplastic large cell lymphomas; ALK: Anaplastic lymphoma kinase; NK: Natural killer

Belli M et al: Rev Bras Hematol Hemoter. 2012

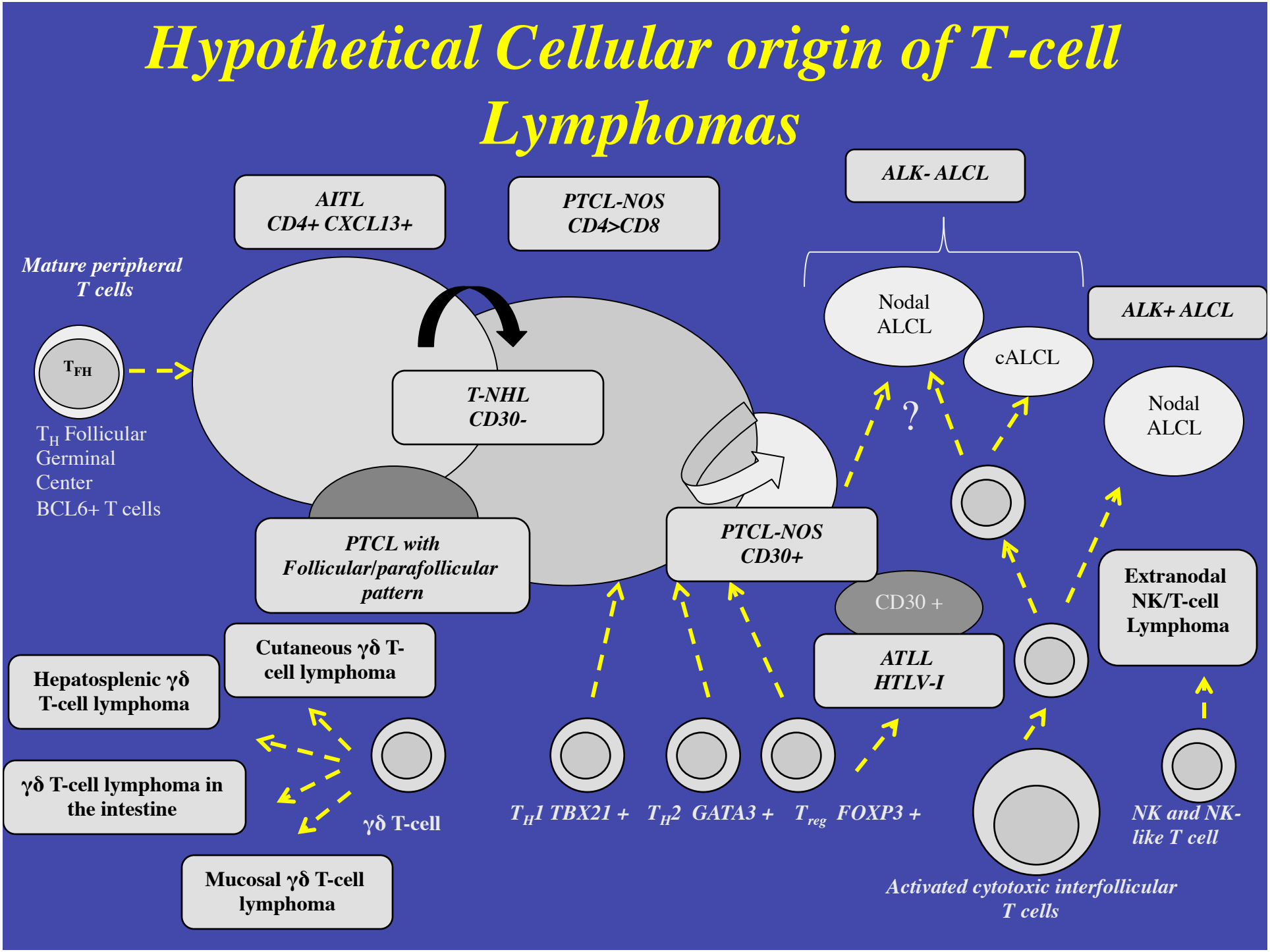
Relative frequencies of T-cell lymphomas



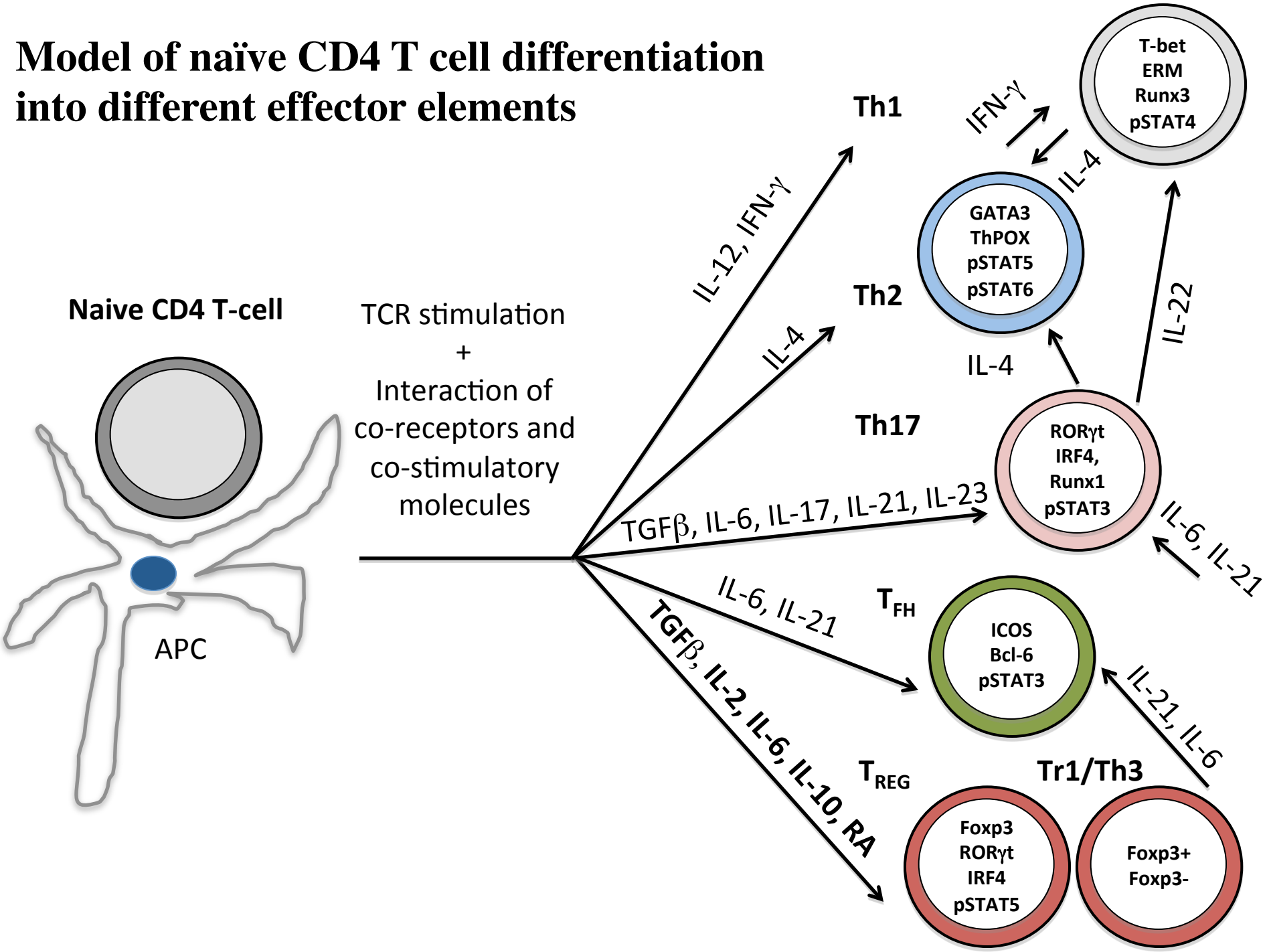
Overall Survival of patients with common Peripheral T-cell Lymphoma subtypes



(Modified from Armitage et al. JCO 2008)

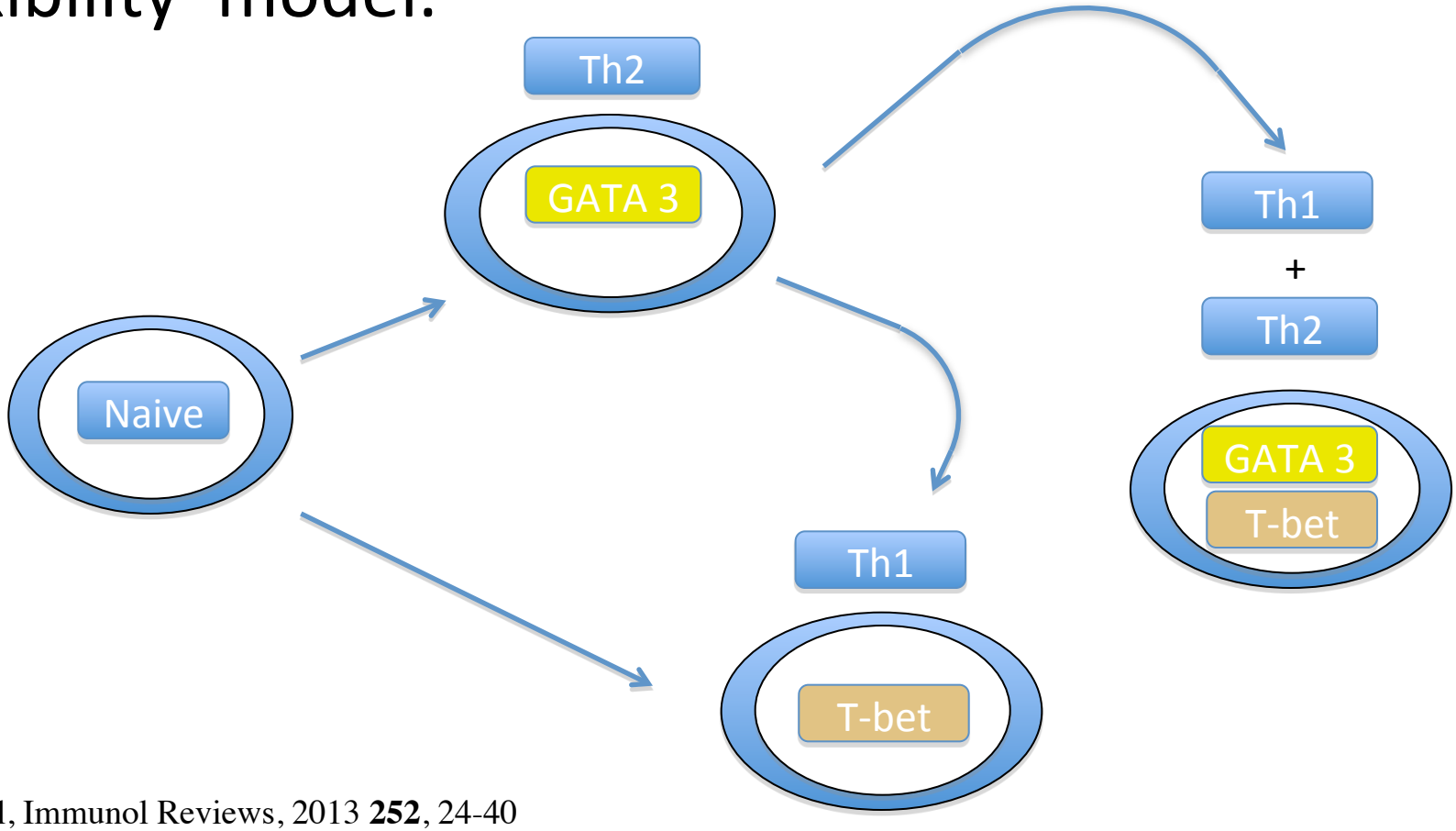

Hypothetical Cellular origin of T-cell Lymphomas
AITL
CD4+ CXCL13+
PTCL-NOS
CD4>CD8
ALK- ALCL
Mature peripheral
T cells
Nodal
ALCL
ALK+ ALCL
cALCL
Nodal
ALCL
T-NHL
CD30-
?
T_FH
T_H Follicular
Germinal
Center
BCL6+ T cells
PTCL with
Follicular/parafollicular
pattern
PTCL-NOS
CD30+
CD30 +
ATLL
HTLV-I
Extranodal
NK/T-cell
Lymphoma
Cutaneous γδ T-
cell lymphoma
Hepatosplenic γδ
T-cell lymphoma
γδ T-cell lymphoma in
the intestine
γδ T-cell
Mucosal γδ T-cell
lymphoma
T_H1 TBX21 +
T_H2 GATA3 +
T_reg FOXP3 +
NK and NK-
like T cell
Activated cytotoxic interfollicular
T cells

Model of naïve CD4 T cell differentiation into different effector elements



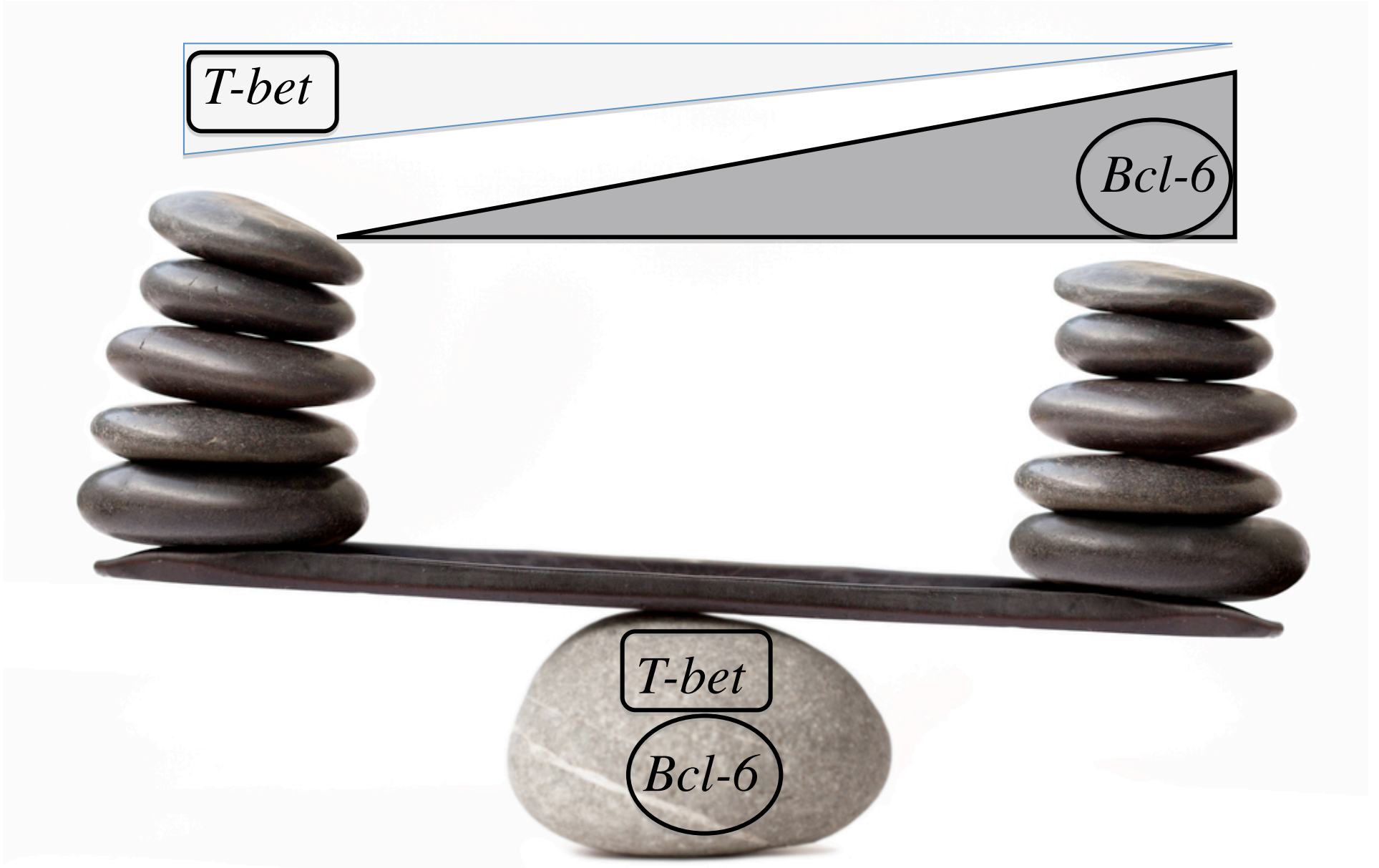
Epigenetic modifications facilitate flexible co-expression of transcription factors permitting flexible responses to offending pathogens

‘Flexibility’ model.



Hahedi et al, Immunol Reviews, 2013 **252**, 24-40

The T-cell phenotypes are regulated by a balanced equilibrium of competing transcription factors



LYMPHOID NEOPLASIA

(Blood. 2014;124(9):1460-1472)

Integrated genomic sequencing reveals mutational landscape of T-cell prolymphocytic leukemia

Mark J. Kiel,[1] Thirunavukkarasu Velusamy,[1] Delphine Rolland,[1] Anagh A. Sahasrabuddhe,[1] Fuzon Chung,[1] Nathanael G. Bailey,[1] Alexandra Schrader,[2] Bo Li,[3] Jun Z. Li,[3,4] Ayse B. Ozel,[4] Bryan L. Betz,[1] Roberto N. Miranda,[5] L. Jeffrey Medeiros,[5] Lili Zhao,[6] Marco Herling,[2] Megan S. Lim,[1] and Kojo S. J. Elenitoba-Johnson[1]

Genomic landscape of cutaneous T cell lymphoma

Jaehyuk Choi, Gerald Goh, Trent Walradt, Bok S Hong, Christopher G Bunick, Kan Chen, Robert D Bjornson, Yaakov Maman, Tiffany Wang, Jesse Tordoff, Kacie Carlson, John D Overton, Kristina J Liu, Julia M Lewis, Lesley Devine, Lisa Barbarotta, Francine M Foss, Antonio Subtil, Eric C Vonderheid, Richard L Edelson, David G Schatz, Titus J Boggon, Michael Girardi & Richard P Lifton

Nature Genetics **47**, 1011–1019 (2015)

The mutational landscape of cutaneous T cell lymphoma and Sézary syndrome

Ana Carolina da Silva Almeida, Francesco Abate, Hossein Khiabanian, Estela Martinez-Escala, Joan Guitart, Cornelis P Tensen, Maarten H Vermeer, Raul Rabadan, Adolfo Ferrando & Teresa Palomero

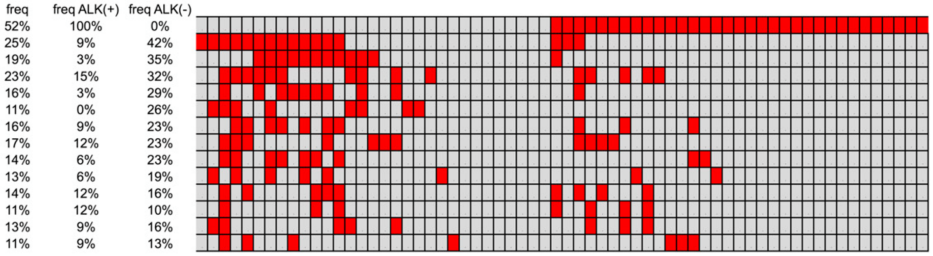
Nature Genetics **47**, 1465–1470 (2015)

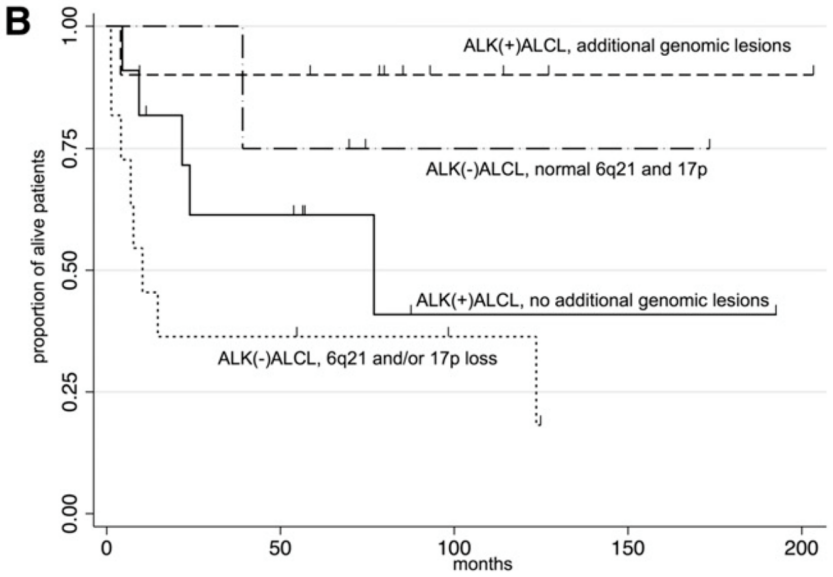
PRDM1/BLIMP1 is commonly inactivated in anaplastic large T-cell lymphoma

Michela Boi,[1] Andrea Rinaldi,[1] Ivo Kwee,[1-3] Paola Bonetti,[1] Maria Todaro,[4] Fabrizio Tabbò,[4] Roberto Piva,[4,5] Paola M. V. Rancoita,[1,2] András Matolcsy,[6] Botond Timar,[6] Thomas Tousseyn,[7] Socorro Maria Rodríguez-Pinilla,[8] Miguel A. Piris,[8] Sílvia Beà,[9] Elias Campo,[9] Govind Bhagat,[10] Steven H. Swerdlow,[11] Andreas Rosenwald,[12] Maurilio Ponzoni,[13] Ken H. Young,[14] Pier Paolo Piccaluga,[15] Reinhard Dummer,[16] Stefano Pileri,[15] Emanuele Zucca,[17] Giorgio Inghirami,[4,5] and Francesco Bertoni[1,17]

Key Points

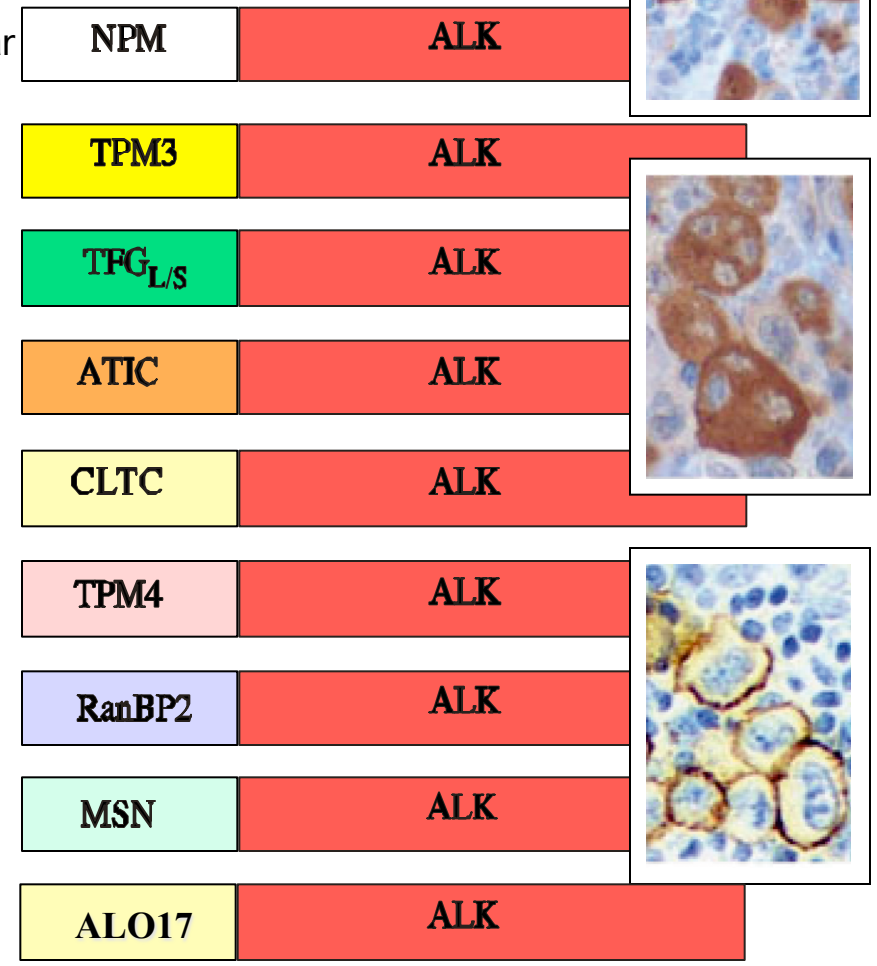
- The commonest lesions in anaplastic large cell lymphomas are losses at 17p13 and at 6q21, concomitant in up to one-quarter of the cases.
- *PRDM1* (BLIMP1) gene (6q21) is inactivated by multiple mechanisms and acts as a tumor suppressor gene in anaplastic large B-cell lymphoma.

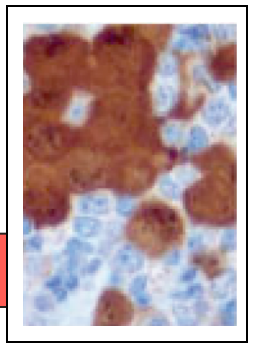




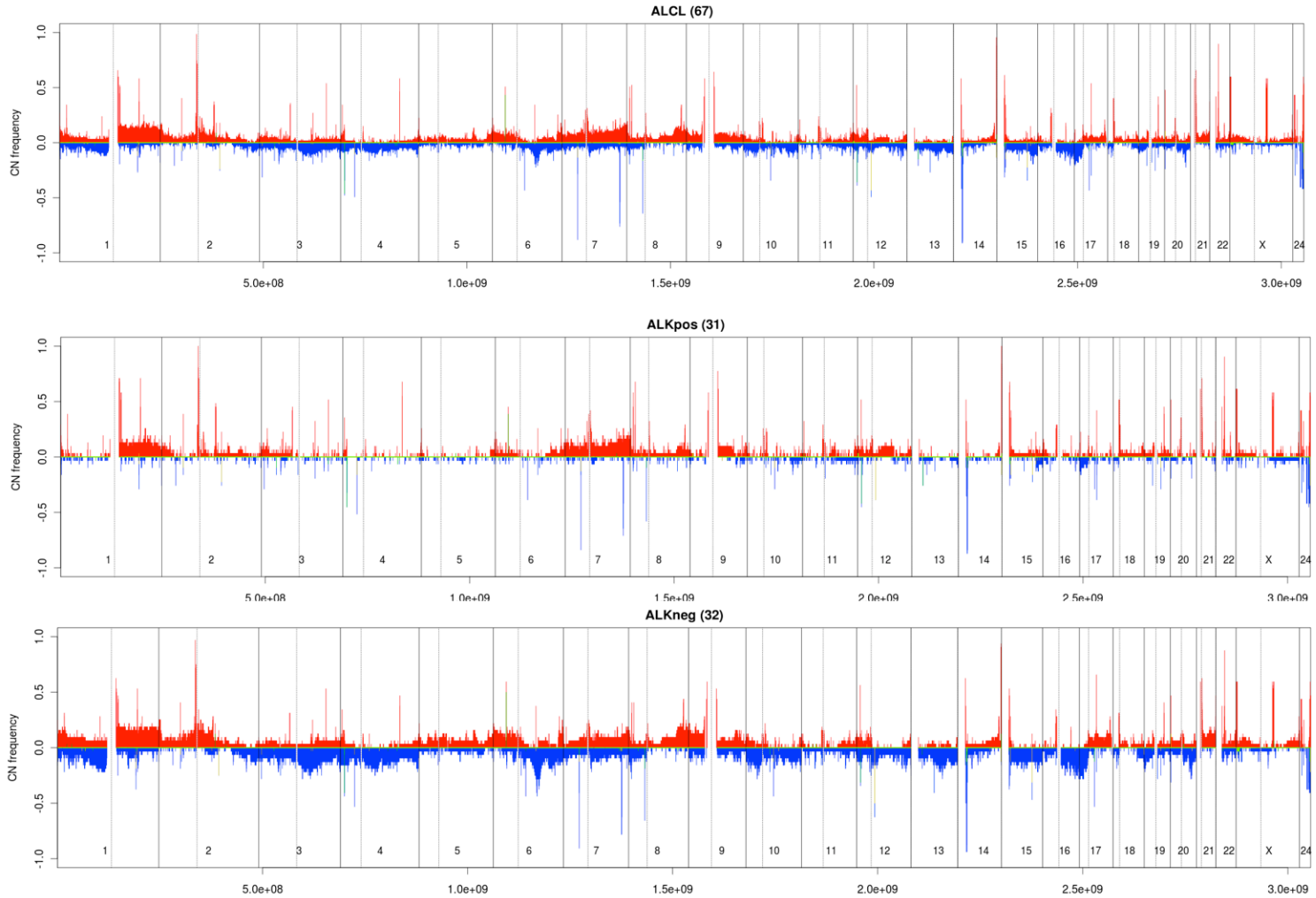
Common fusion proteins of ALK+ ALCL

Translocation	Frequency (NHL)	Localization
t(2;5)(p23;q35)	70-80%	Cytoplasmic/Nuclear nucleolar
t(1;2)(q25;p23)	10-20%	Cytoplasmic
t(2;3)(p23;q21)	2-5%	Cytoplasmic
inv(2)(p23;q35)	2-5%	Cytoplasmic
t(2;17)(p23;q23)	2-5%	Cytoplasmic
t(2;19)(p23;q13,1)	-	Cytoplasmic
t(2;2)(p23;q11-13)?	-	Nuclear
or inv(2)(p23;q11-13)?	-	membrane
t(X;2)(q11-12;p23)	-	Cell-Membrane
t(2;17)(p23;q25)	2-6%	Cytoplasmic





Many T-cell lymphomas have a unique genotype and recurrent lesions

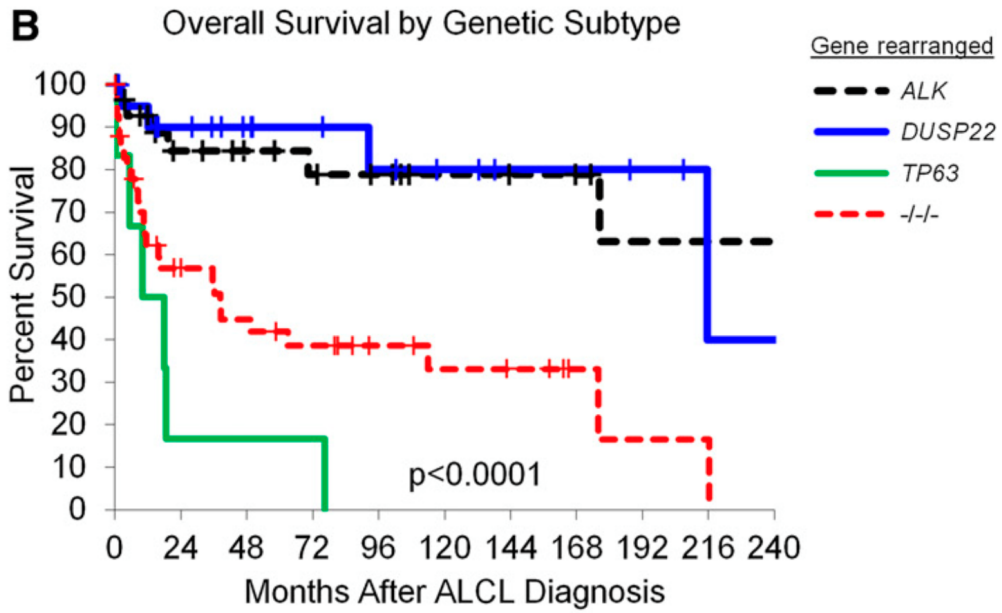


ALK-negative anaplastic large cell lymphoma is a genetically heterogeneous disease with widely disparate clinical outcomes

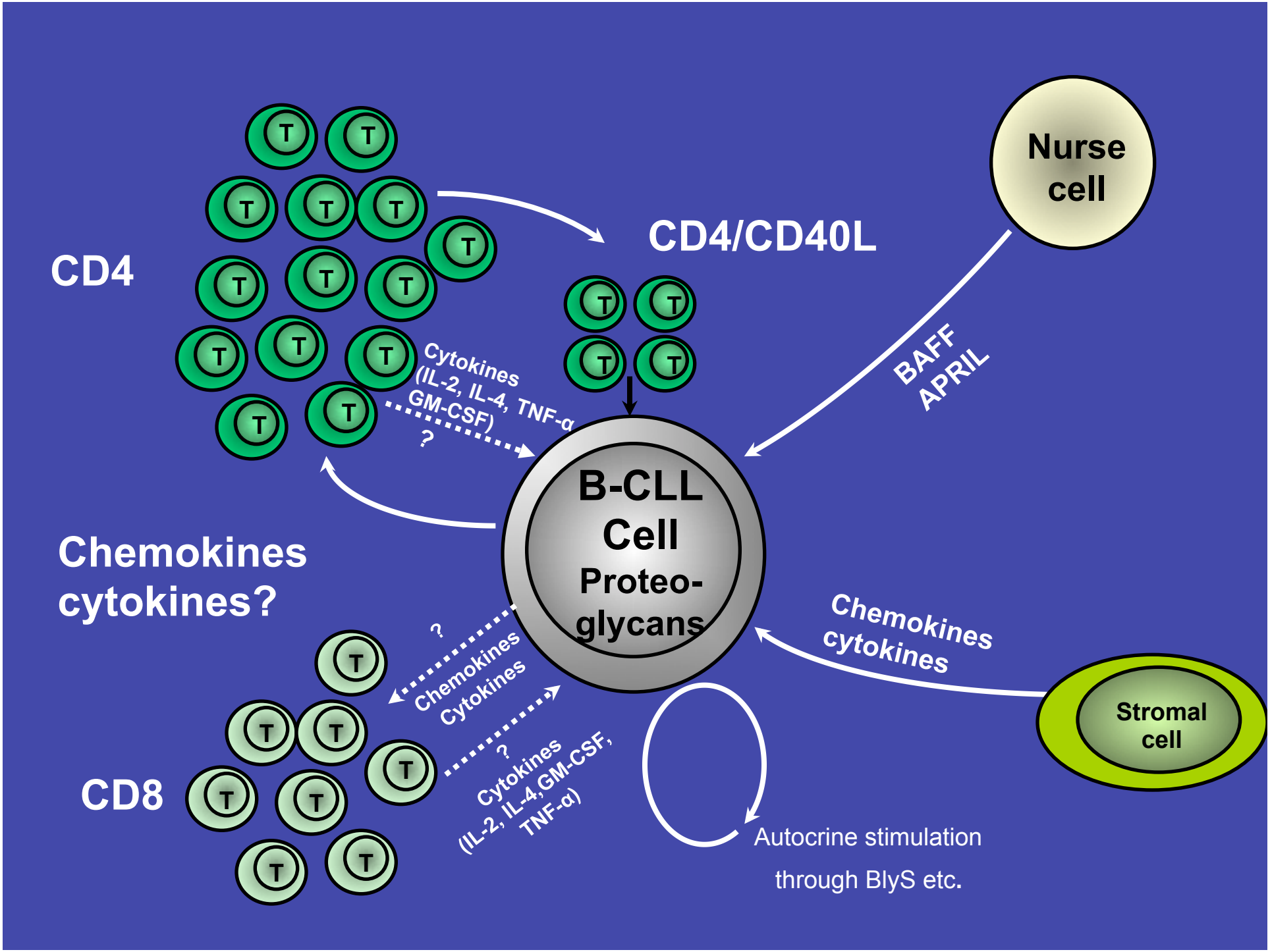
Edgardo R. Parrilla Castellar,[1] Elaine S. Jaffe,[2] Jonathan W. Said,[3] Steven H. Swerdlow,[4] Rhett P. Ketterling,[1] Ryan A. Knudson,[1] Jagmohan S. Sidhu,[5] Eric D. Hsi,[6] Shridevi Karikehalli,[7] Liuyan Jiang,[8] George Vasmatzis,[9] Sarah E. Gibson,[4] Sarah Ondrejka,[6] Alina Nicolae,[2] Karen L. Grogg,[1] Cristine Allmer,[10] Kay M. Ristow,[11] Wyndham H. Wilson,[12] William R. Macon,[1] Mark E. Law,[1] James R. Cerhan,[10] Thomas M. Habermann,[11] Stephen M. Ansell,[11] Ahmet Dogan,[1] Matthew J. Maurer,[10] and Andrew L. Feldman[1]

Key Points

- ALK-negative ALCLs have chromosomal rearrangements of *DUSP22* or *TP63* in 30% and 8% of cases, respectively.
- *DUSP22*-rearranged cases have favorable outcomes similar to ALK-positive ALCLs, whereas other genetic subtypes have inferior outcomes.



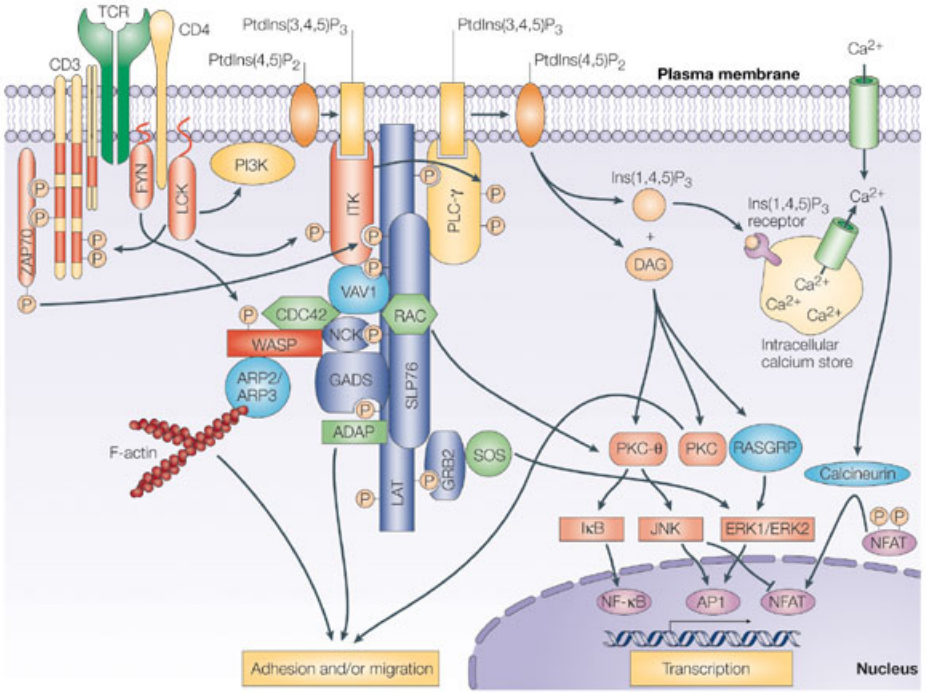
***DUSP22-IRF4* locus**

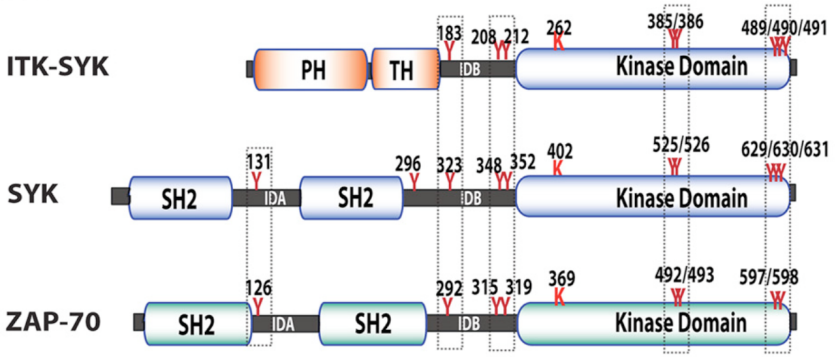

CD4
CD4/CD40L
Nurse cell
BAFF
APRIL
Cytokines
(IL-2, IL-4, TNF-α
GM-CSF)
?
B-CLL
Cell
Proteo-
glycans
Chemokines
cytokines?
?
Chemokines
Cytokines
?
Cytokines
(IL-2, IL-4,GM-CSF,
TNF-α)
CD8
Chemokines
cytokines
Stromal
cell
Autocrine stimulation
through BlyS etc.

TCR signaling and the host contribution in the pathogenesis of T-cell neoplasms

- Pre-TCR expression cooperates and T cell receptor/antigen stimulation have been proven to foster T cell transformation in mice carrying the TEL-JAK2 fusion or STAT5, respectively (dos Santos 2007; Kelly 2003)
- Super-antigen mediated activation has been suggested to play a pathogenetic role in cutaneous T-cell lymphoma (Vb2:Jackow 1997)
- Gluten exposure leads to inflammation and T cell expansion which proceed EATL
- T-NHL display a transcriptome that is consistent with a TCR signaling, particularly in low-grade entities (Geissinger 2010)

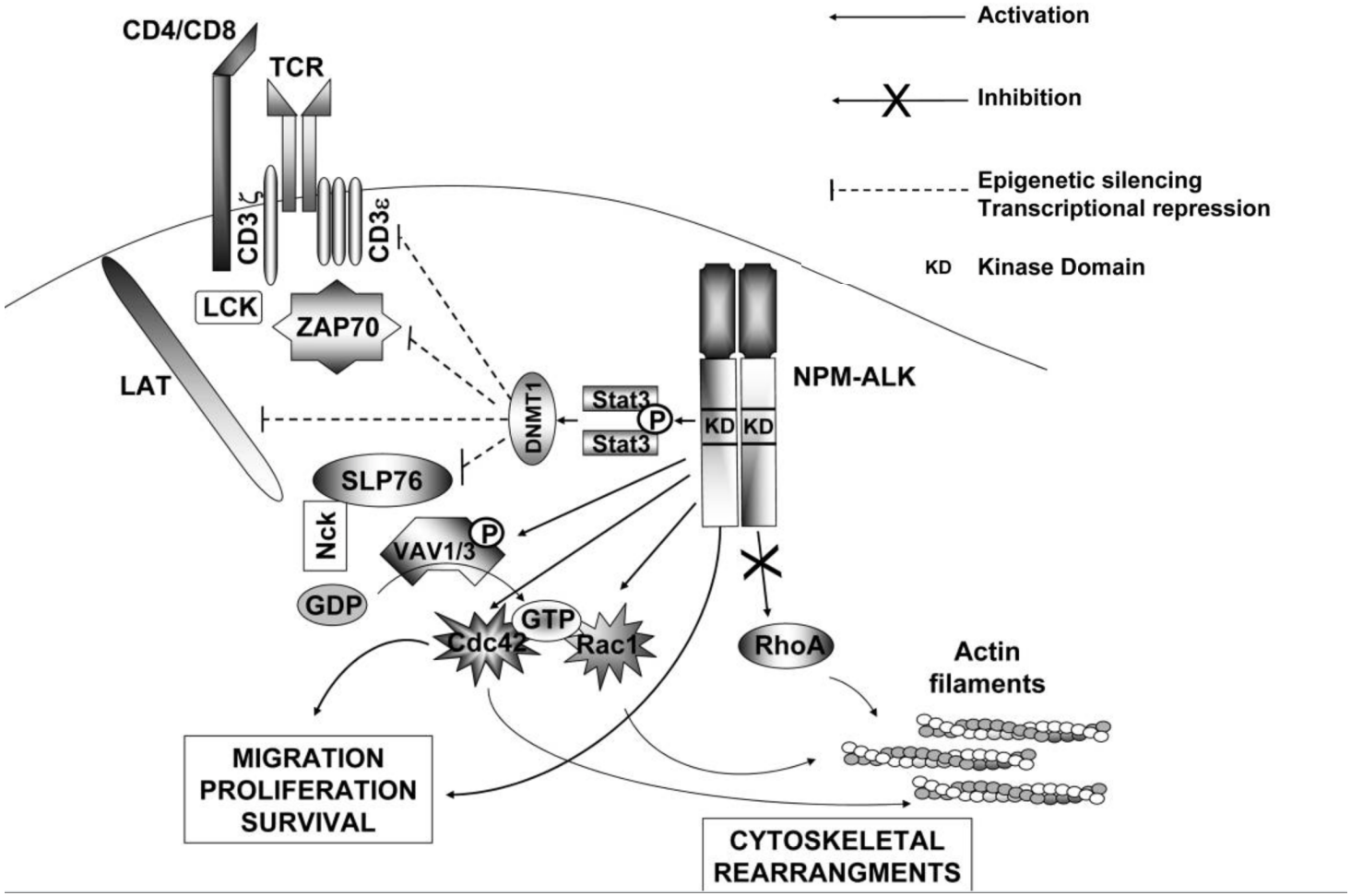
The fusion kinase ITK-SYK mimics a T cell receptor signal and drives oncogenesis in conditional mouse models of peripheral T cell lymphoma





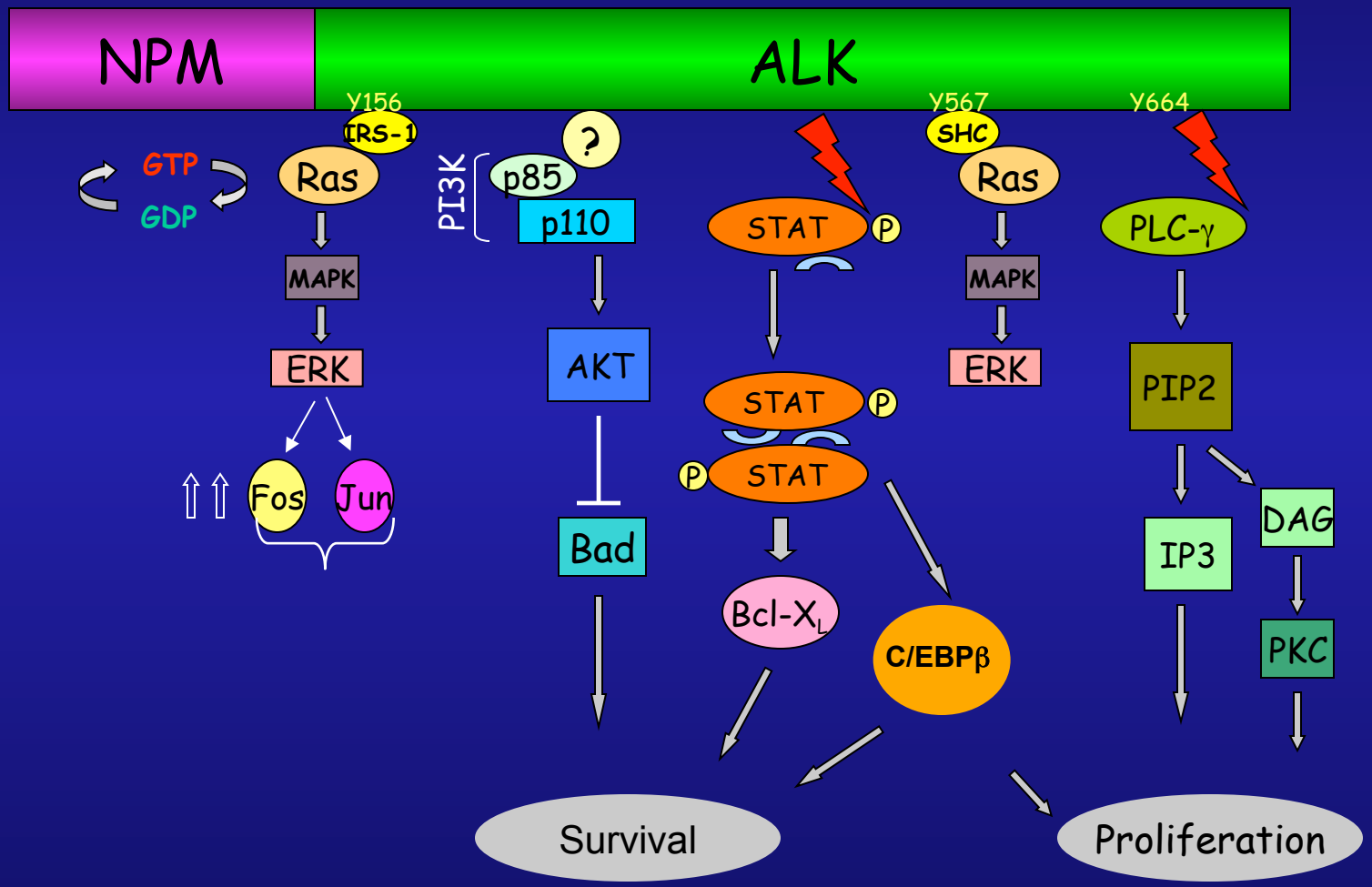
Pechloff K. et al J. Exp. Med. Vol. 207 No. 5 1031-1044

NPM-ALK oncogenic tyrosine kinase controls T cell identity by transcriptional regulation and epigenetic silencing in lymphoma cells

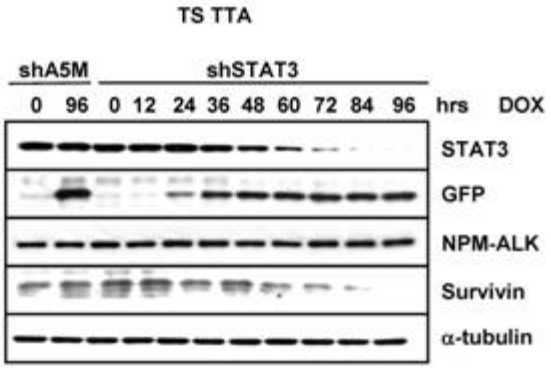


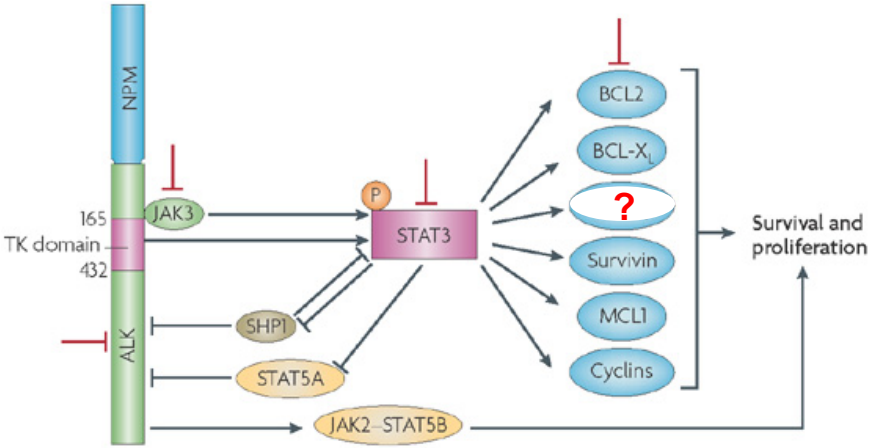
Ambrogio C et al. *Cancer Res*. 2009 November 15; 69: 8611–8619

NPM-ALK signaling pathways

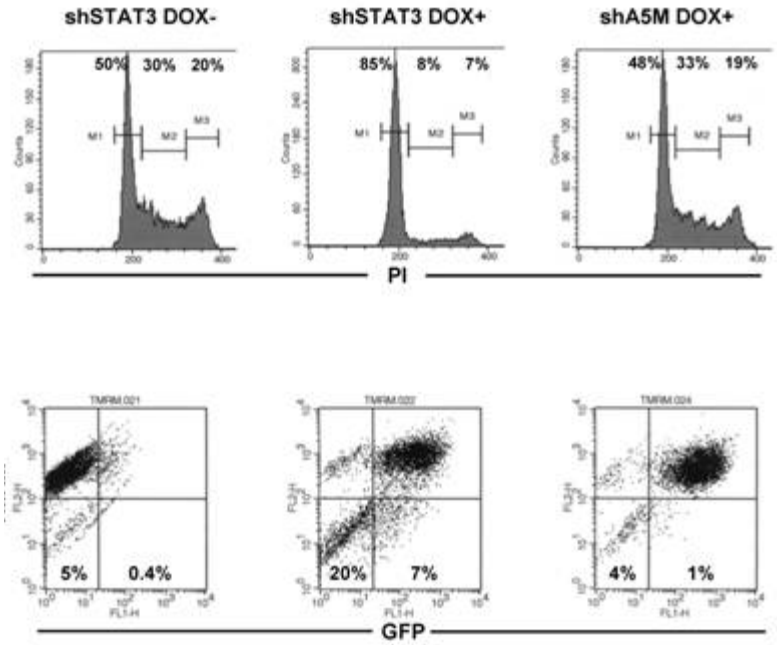


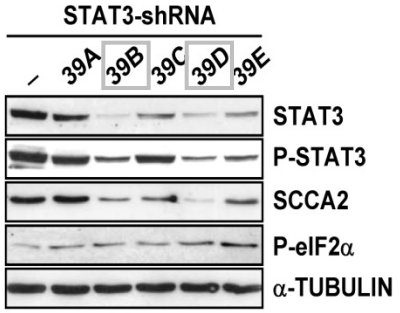
STAT3 silencing induces first cell cycle arrest followed by cell death

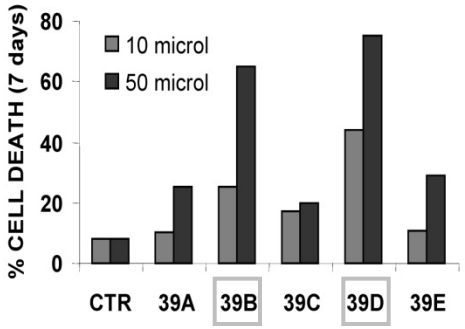




Chiarle et al. Nature Rev Cancer 2008



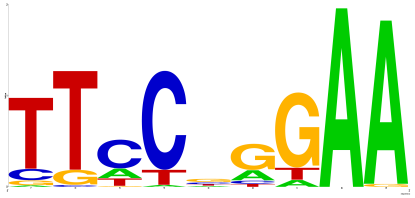




Piva et al. JC0, 2010

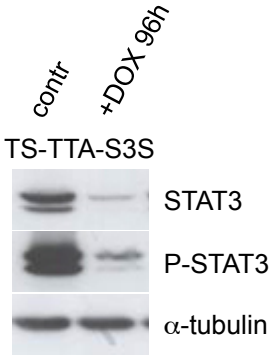
STAT3 regulates the expression of CD30

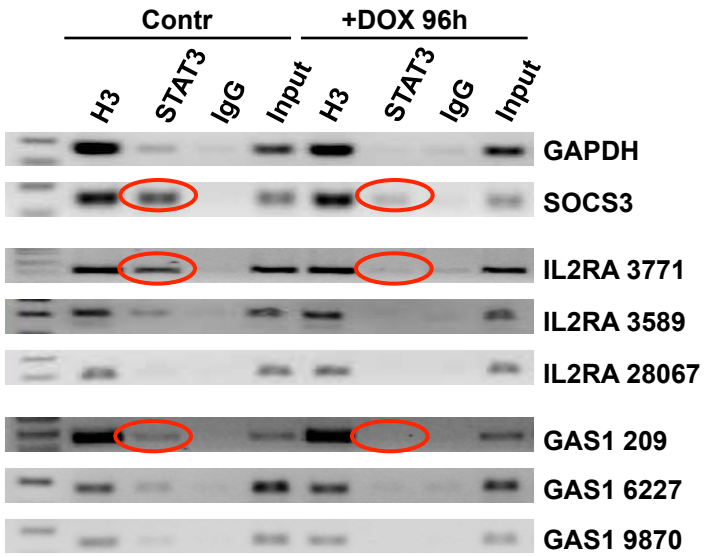
Position Weight Matrix approach

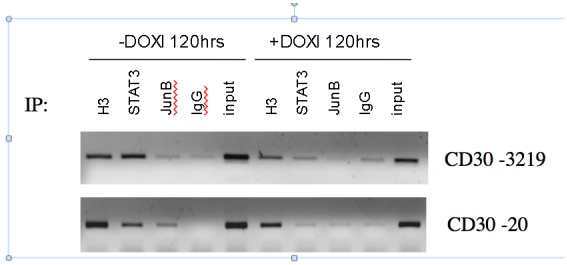


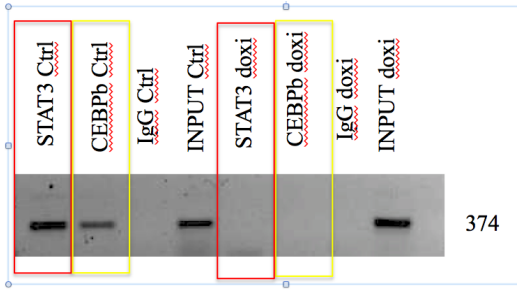
	STAT3 CONSENSUS SITES		
GENE	**POSITION**	**SCORE**	**CONSERVATION**
TNFRSF8	-3219	10,18	Bt
	-1257	10,28	Cf
	-374	*	
	-20	12,96	
	19238	9,94	Bt
GAS1	-209	14,53	
	-6227	10,24	
	-9870	11,11	
SCCA2	-1538	10,28	
	-2885	10,47	
	-2963	10,28	
	-3011	9,95	
	-4159	11,87	
	-6224	10,47	
ICOS	-2448	10,81	Bt
	1815	10,47	Mm
	12765	10,24	Cf, Bt
	14486	10,58	Bt
IL2RA	-3771	11,11	Cf, Bt
	472	11,87	Bt
	3589	11,11	Mm, Cf, Bt
	11008	9,87	Cf, Bt
	23677	9,95	Bt
	25962	11,87	Cf
	28067	12,96	Cf, Bt
HSD17B7	-6685	9,72	Cf
	-3473	10,91	Cf
SGK	13146	10,18	Mm
	39382	10,22	Mm, Bt
RGS16	-6374	10,58	Mm, Cf, Bt
	-4789	9,95	Bt
	-2251	10,81	Cf, Bt
	941	12,96	Bt

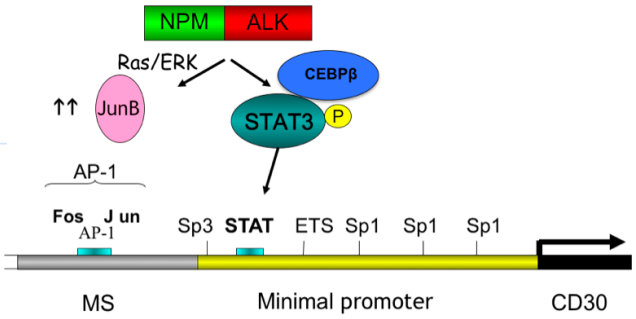
Validation of STAT3 binding sites by CHIP



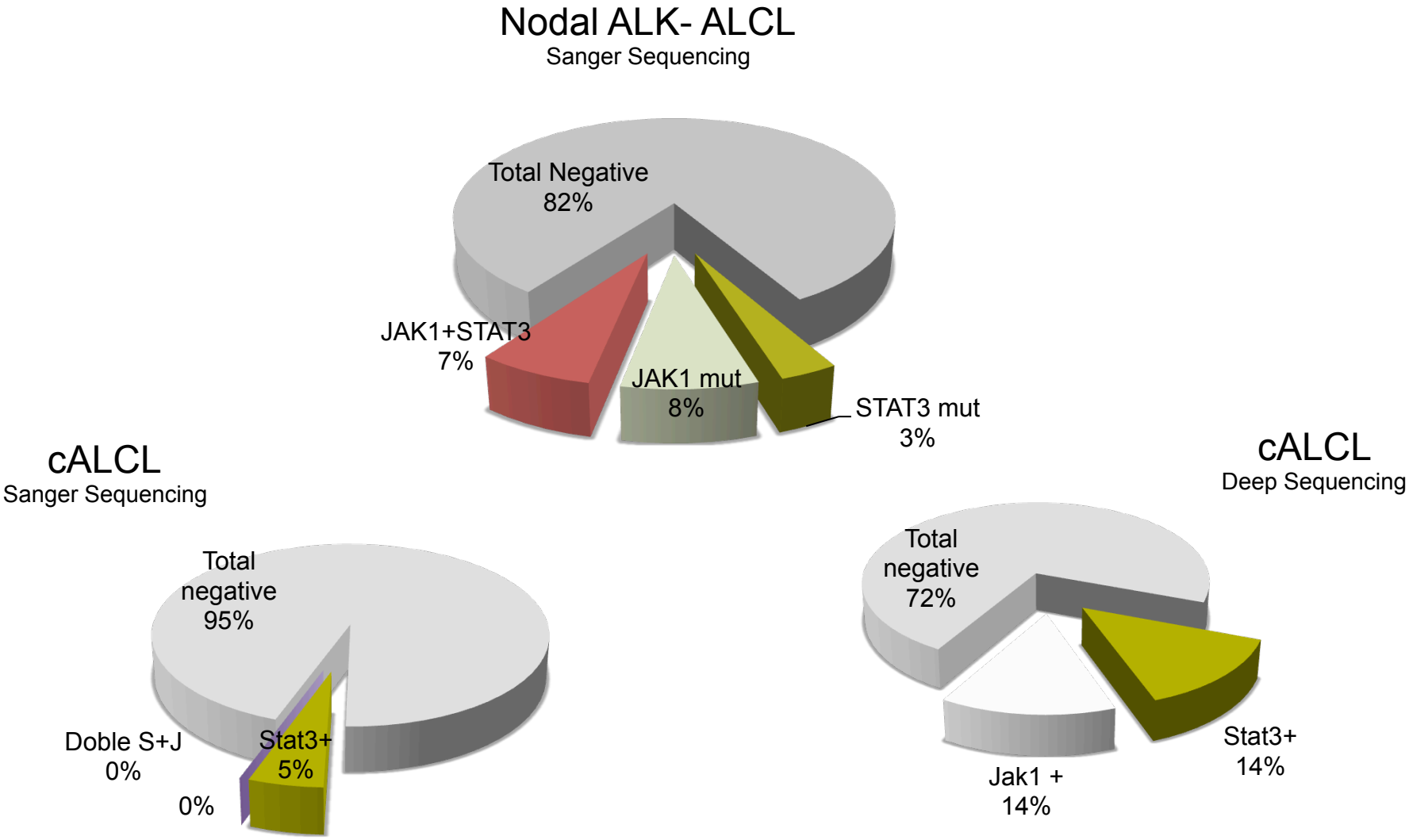




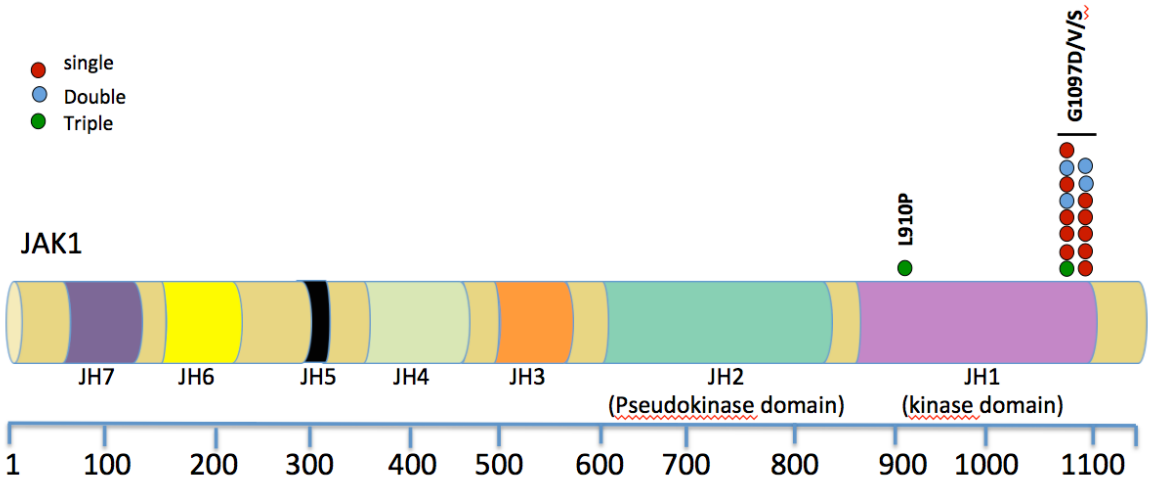


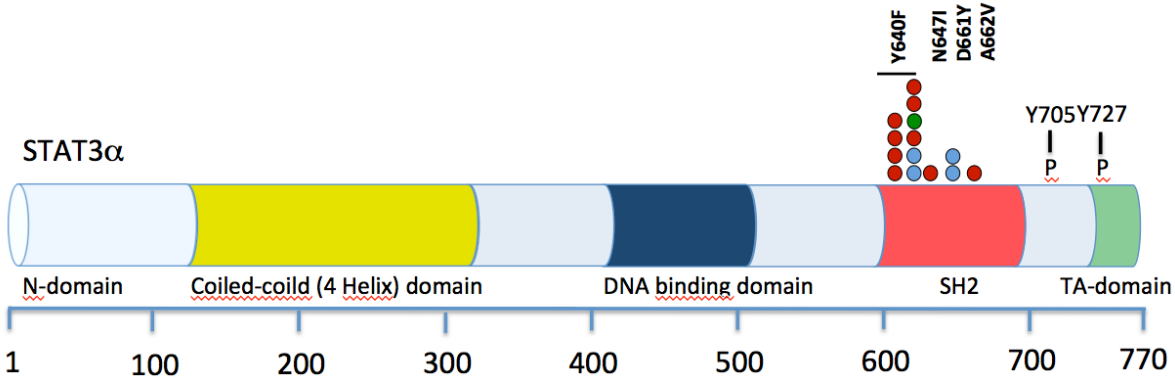


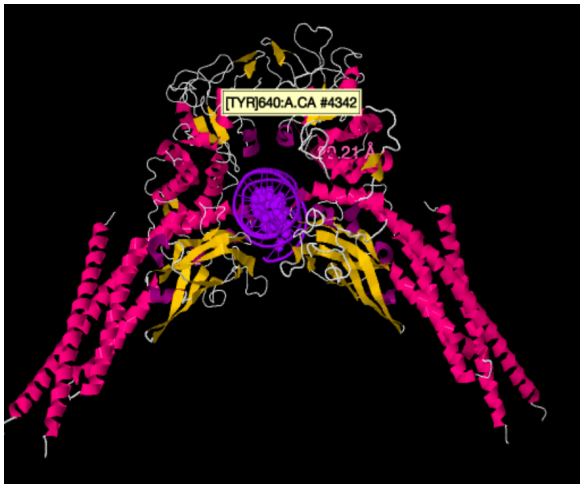
JAK1 and STAT3 are frequently mutated in systemic and cutaneous ALCL



JAK1 and/or STAT3 mutations are frequently found in ALK- ALCL

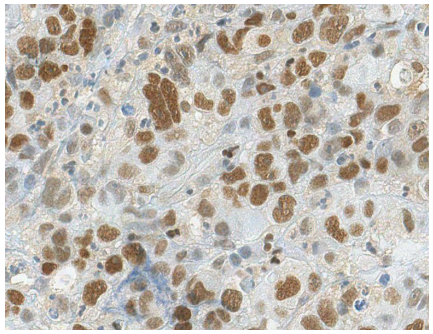




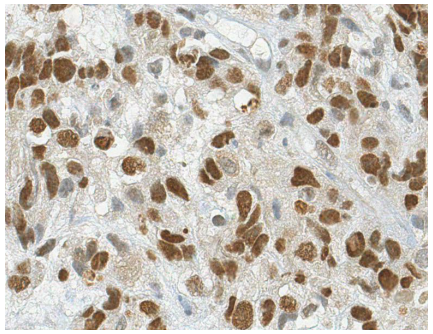


pSTAT3 expression defines a subset of ALK- ALCL

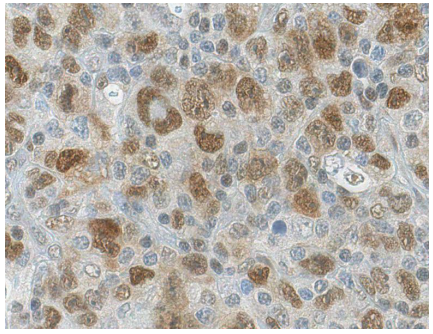
WT JAK1/STAT3



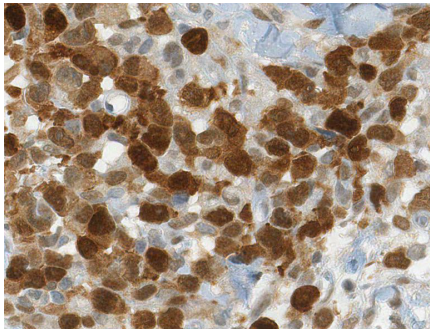
A662V STAT3



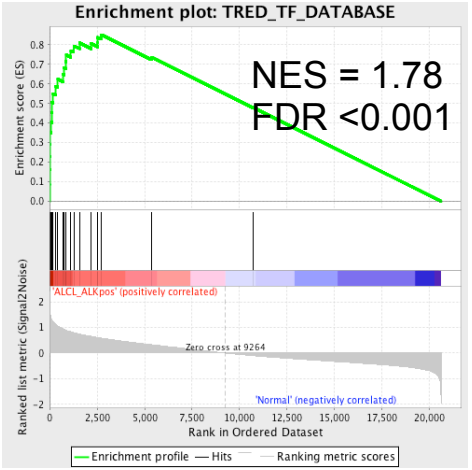
G1097D JAK1



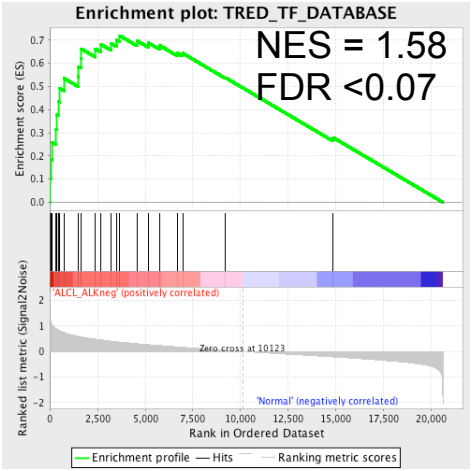
Y640F STAT3



ALCL ALK+ vs Normal



ALCL ALK- vs Normal

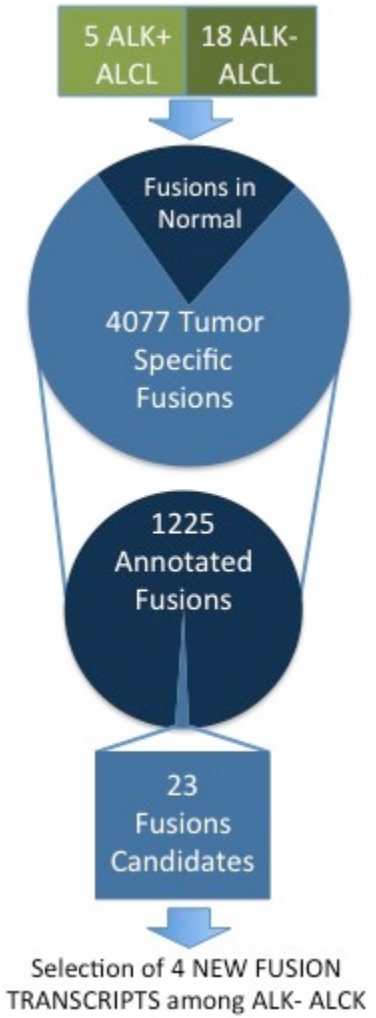


How is frequently deregulated the JAK/STAT pathway in T-cell lymphomas?

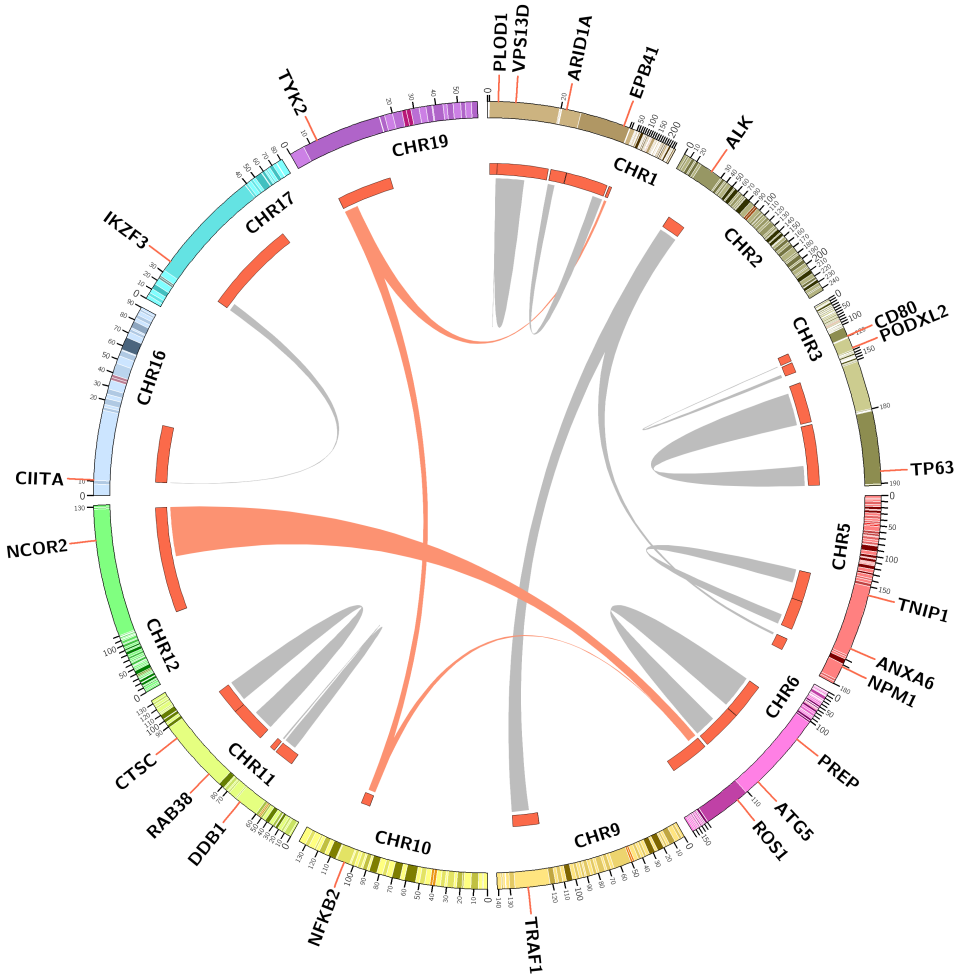
JAK STAT signaling pathway in T-cell lymphoproliferative disorders		
Gene	**Neoplasms**	**Reference**
JAK1	T-ALL	Porcu, 2009; Mullighan, 2009
JAK1	CTCL	Perez, 2014
JAK1	ALK- ALCL	Crescenzo, 2015
JAK1	T-PLL	Bellenager 2014
JAK1	ATLL	Kataoka 2015
JAK2	T-ALL	Mullighan, 2009; Roncero, 2015
JAK2 fusions	T-ALL	Onnebo, 2012
JAK3	CTCL	Perez, 2014; McGirt 2015
JAK3	T-ALL	Mullighan, 2009;Bains, 2012; Kawashima 2015
JAK3	NKTCL	Koo, 2012
JAK3	T-PLL	Bellenager 2014
JAK3	ATLL	Kataoka 2015
STAT3	Gamma-delta PTCL	Kucuk 2015
STAT3	NKTCL	Koskela, 2012; Ohgami 2013
STAT3	ALK- ALCL	Crescenzo, 2015
STAT3	AITL	Odejide, 2014
STAT3	ATLL	Kataoka 2015
STAT5B	Gamma-delta PTCL	Kucuk 2015
STAT5B	CTCL and Sezary	Perez, 2014
PTPRC	T-ALL	Porcu, 2012
PTPN2	PTCL-NOS	Kleppe, 2011
PTPN2	T-ALL	Tartaglia 2004 ; Kleppe 2010

ALK- ALCL display novel recurrent TK translocations

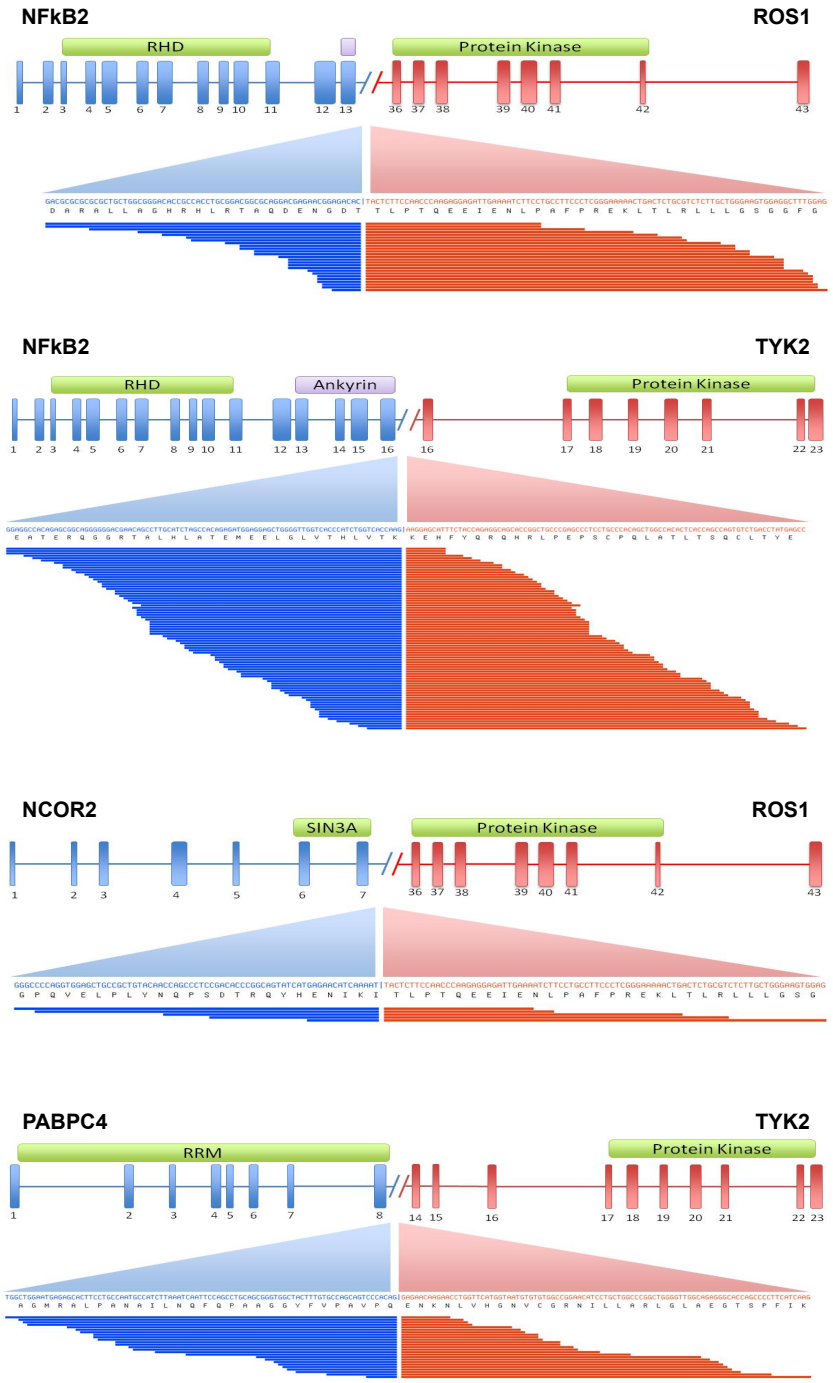
A



B



A



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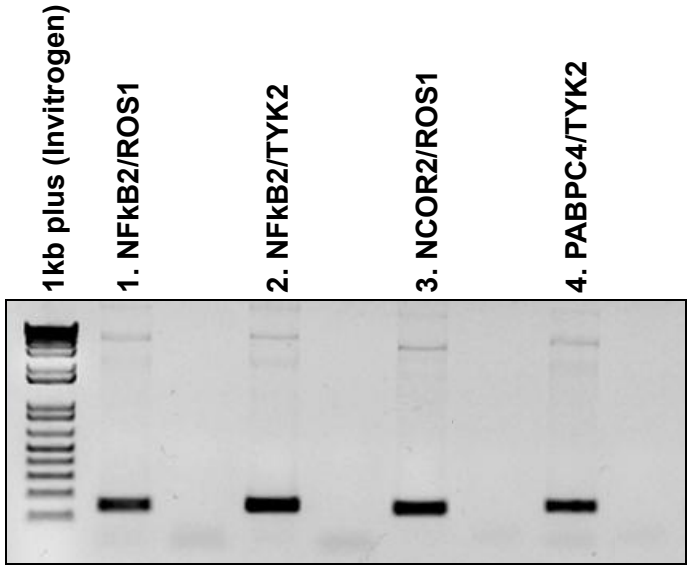
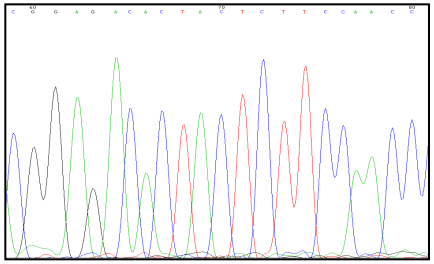
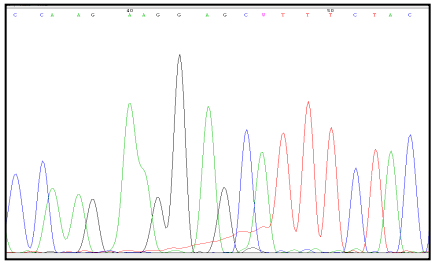


C

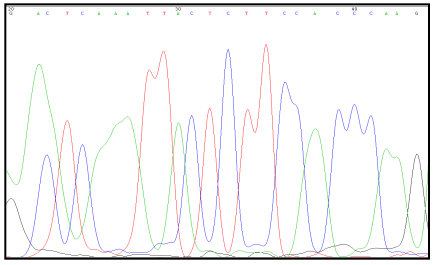
1. NFkB2/ROS1



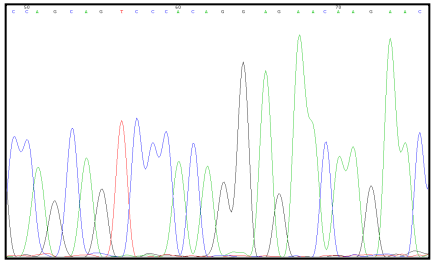
2. NFkB2/TYK2



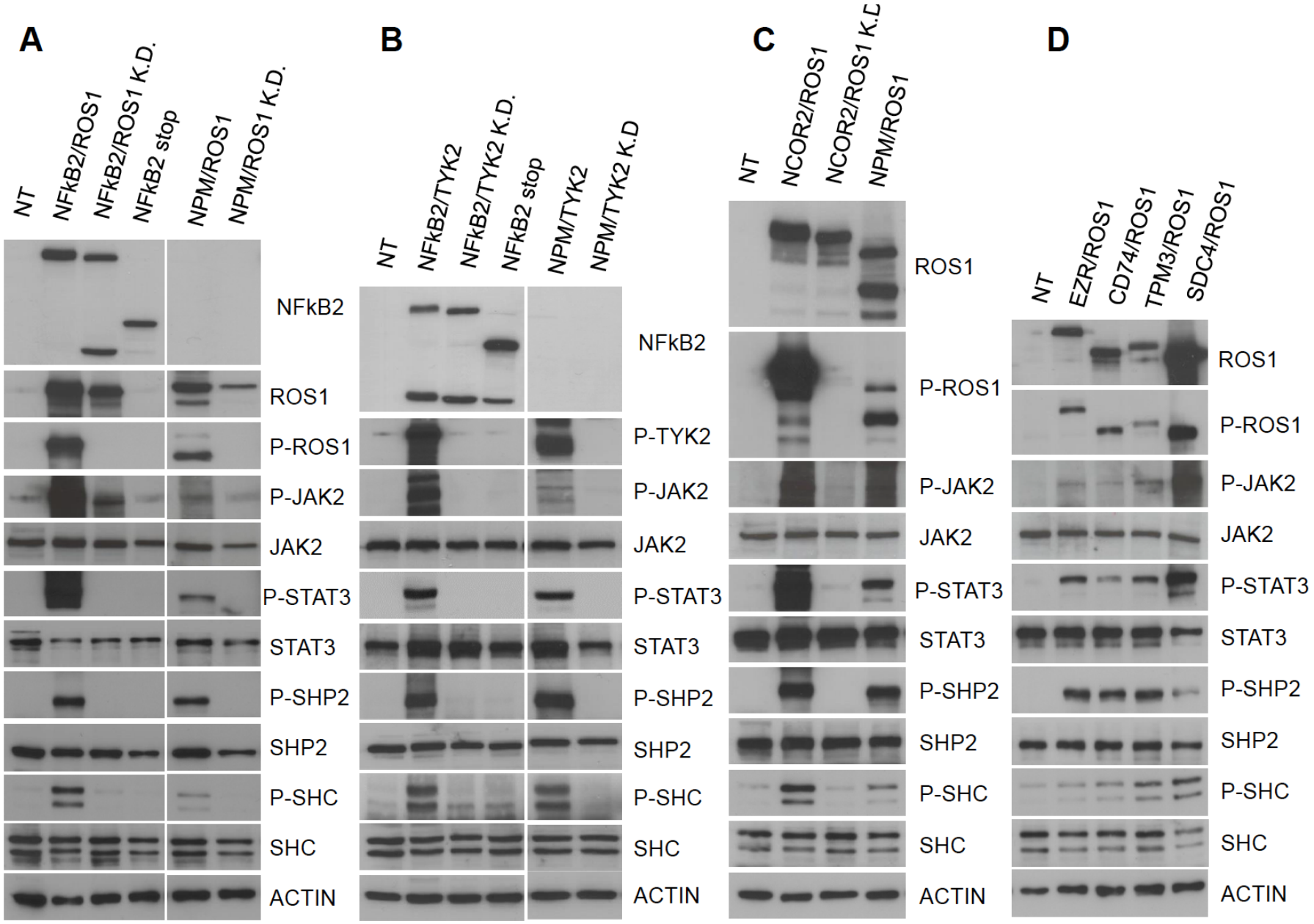
3. NCOR2/ROS1



4. PABPC4/TYK2

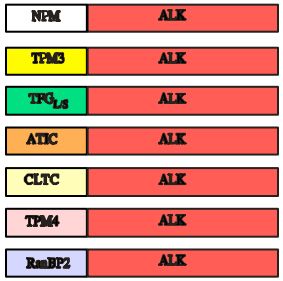


ALK- ALCL bear novel TK translocations

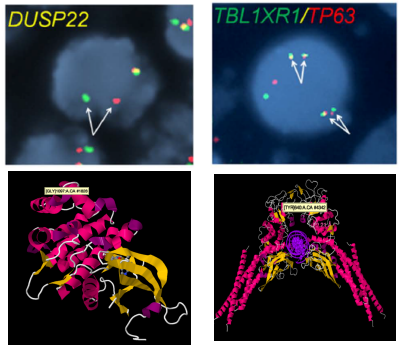


ALCL Subtypes

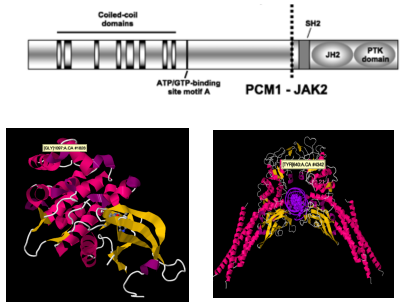
ALK + ALCL



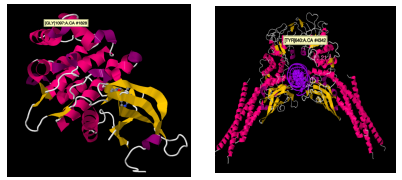
ALK- ALCL

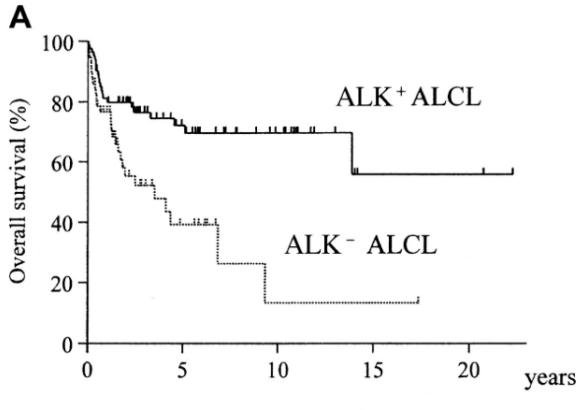


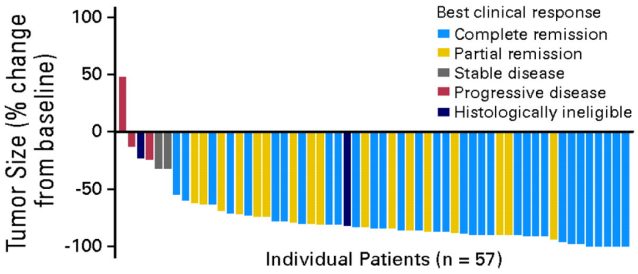
Cutaneous ALCL



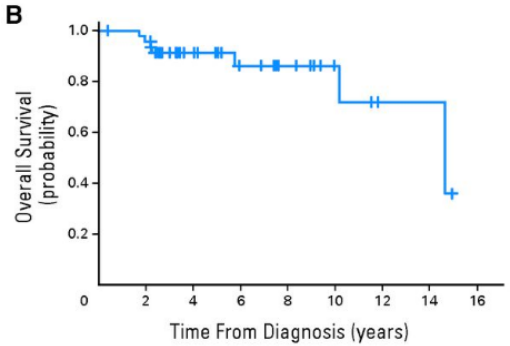
Breast implant ALCL

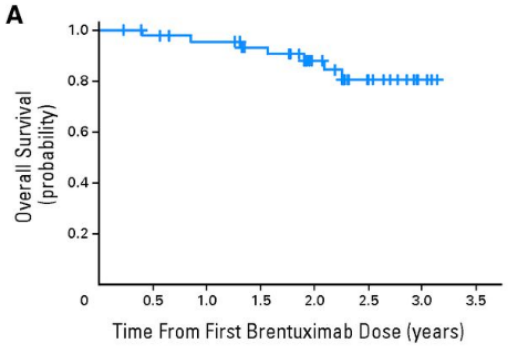




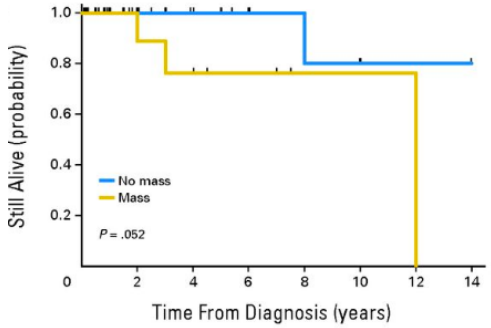


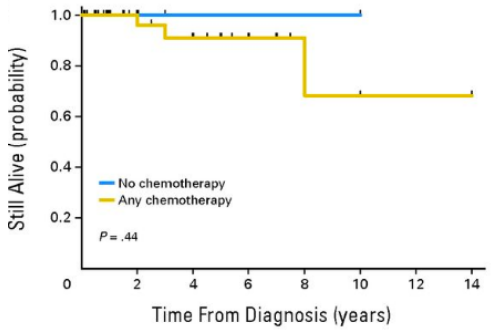
Pro B et al, JCO 2012





Duvic M et al, JCO 2015





Miranda RN et al, JCO 2014

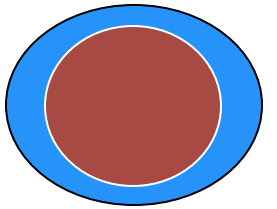
ALCL models

1th initial tumorigenic events

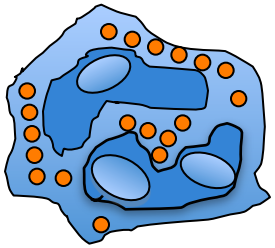
ALK translocation
TYK2/ROS fusions
Activating JAK and STAT mutations
ERBB4 (ATI)
DUSP22
X and Y ???

Additional tumorigenic events

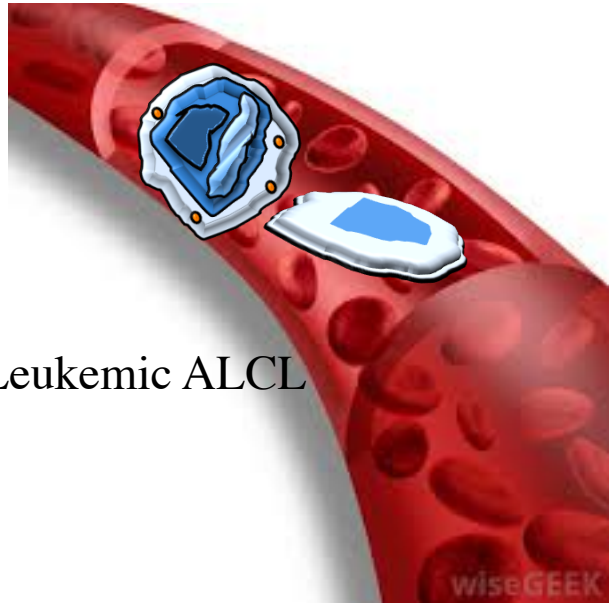
Blimp1 ko
TP53/TP63
MYC deregulation



Cytotoxic T lymphocytes ?
or
Mature CD4 or CD8 T lymphocytes?

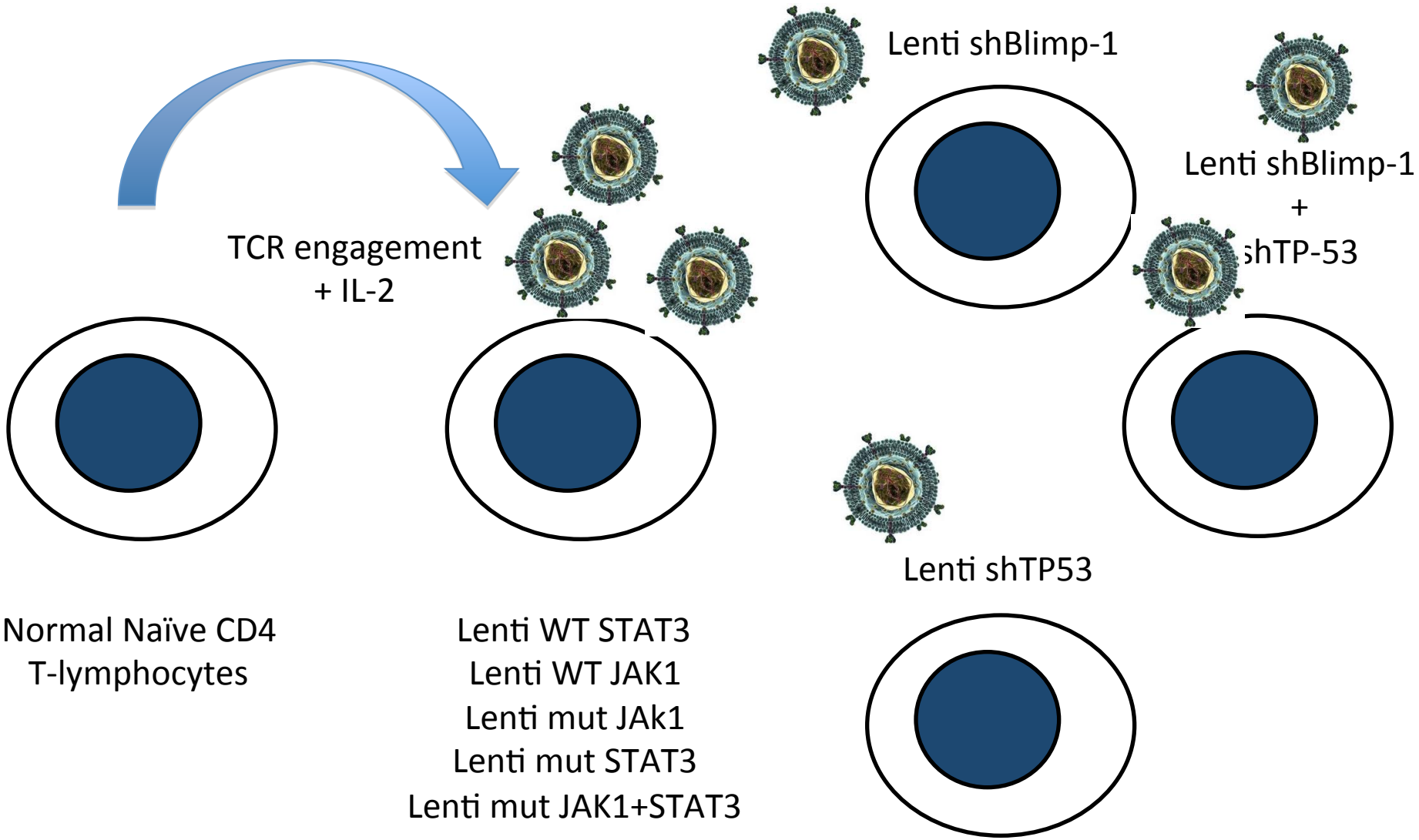


Cytotoxic ALCL

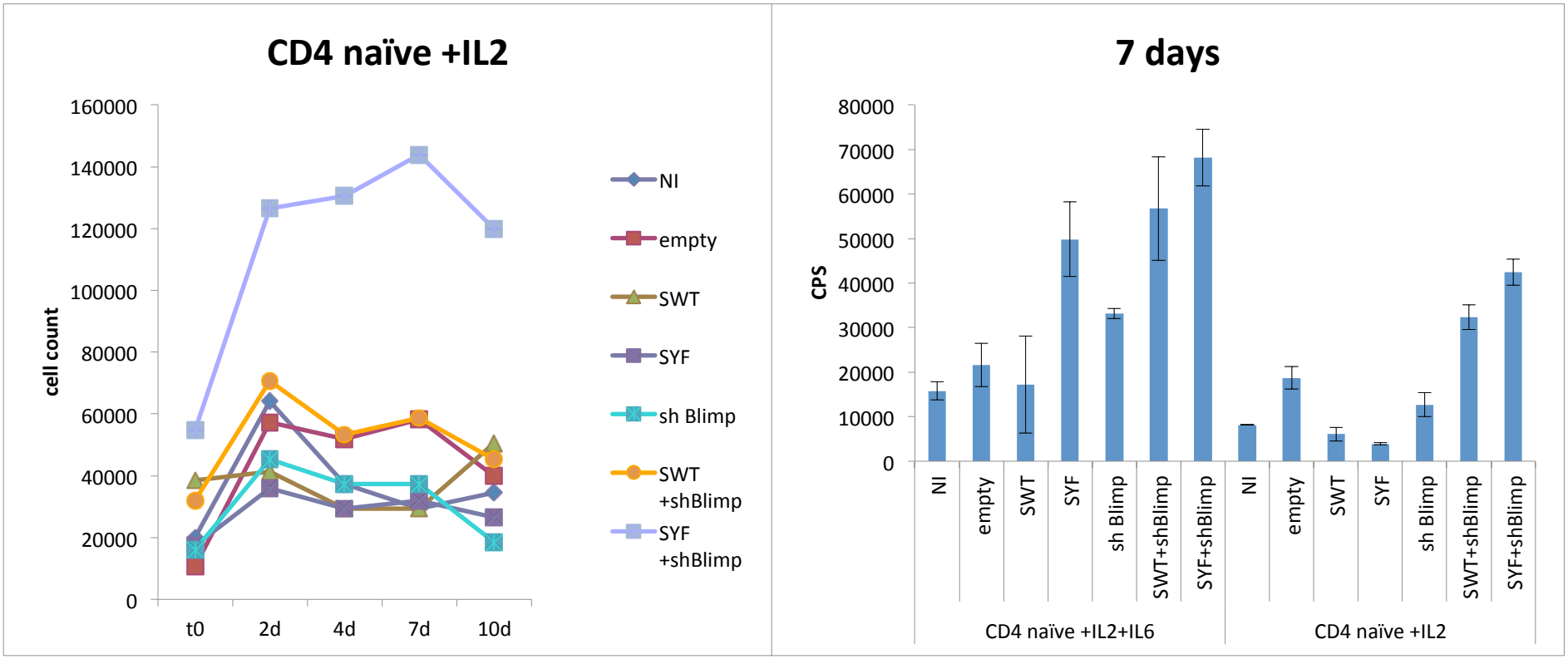


Leukemic ALCL

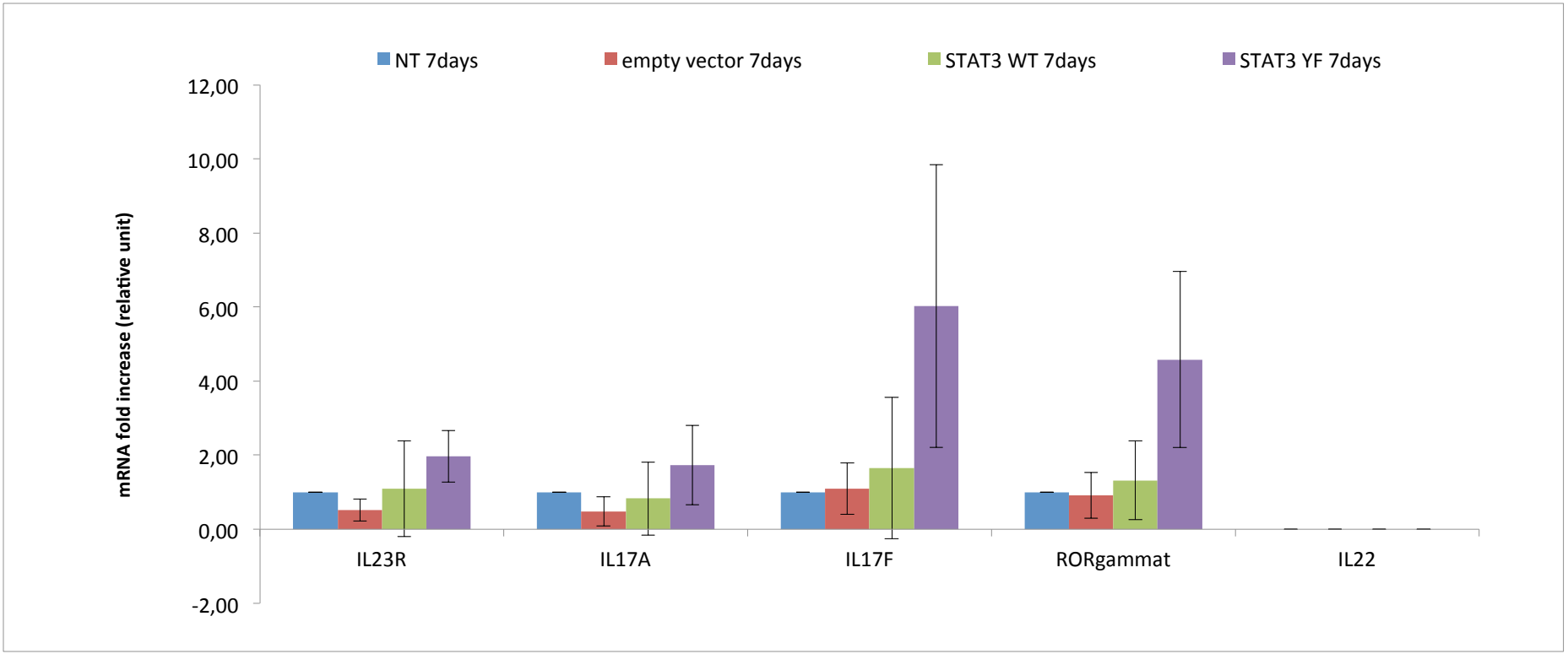
Clonal evolution: sequential genomics acquisition



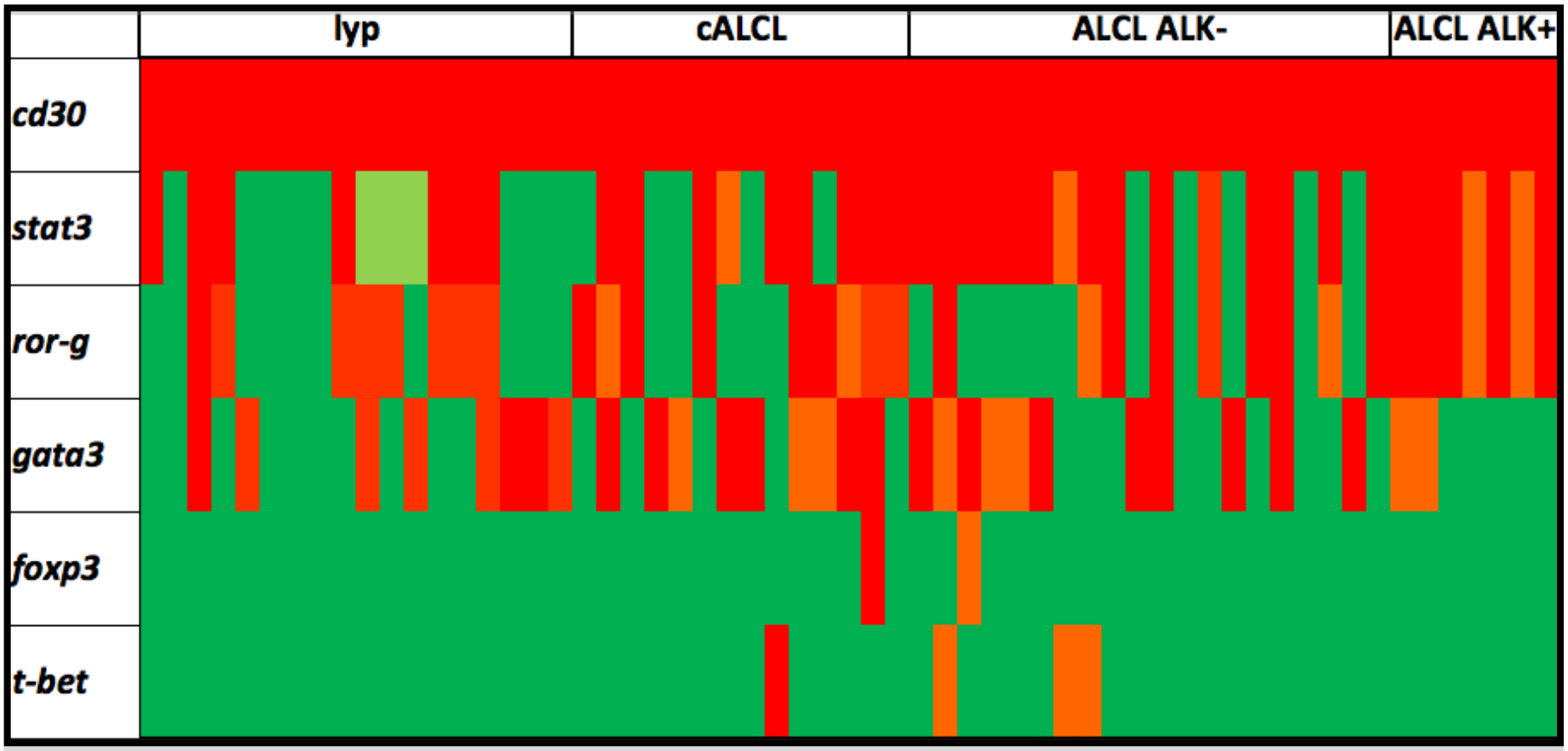
Clonal evolution: sequential genomics acquisition



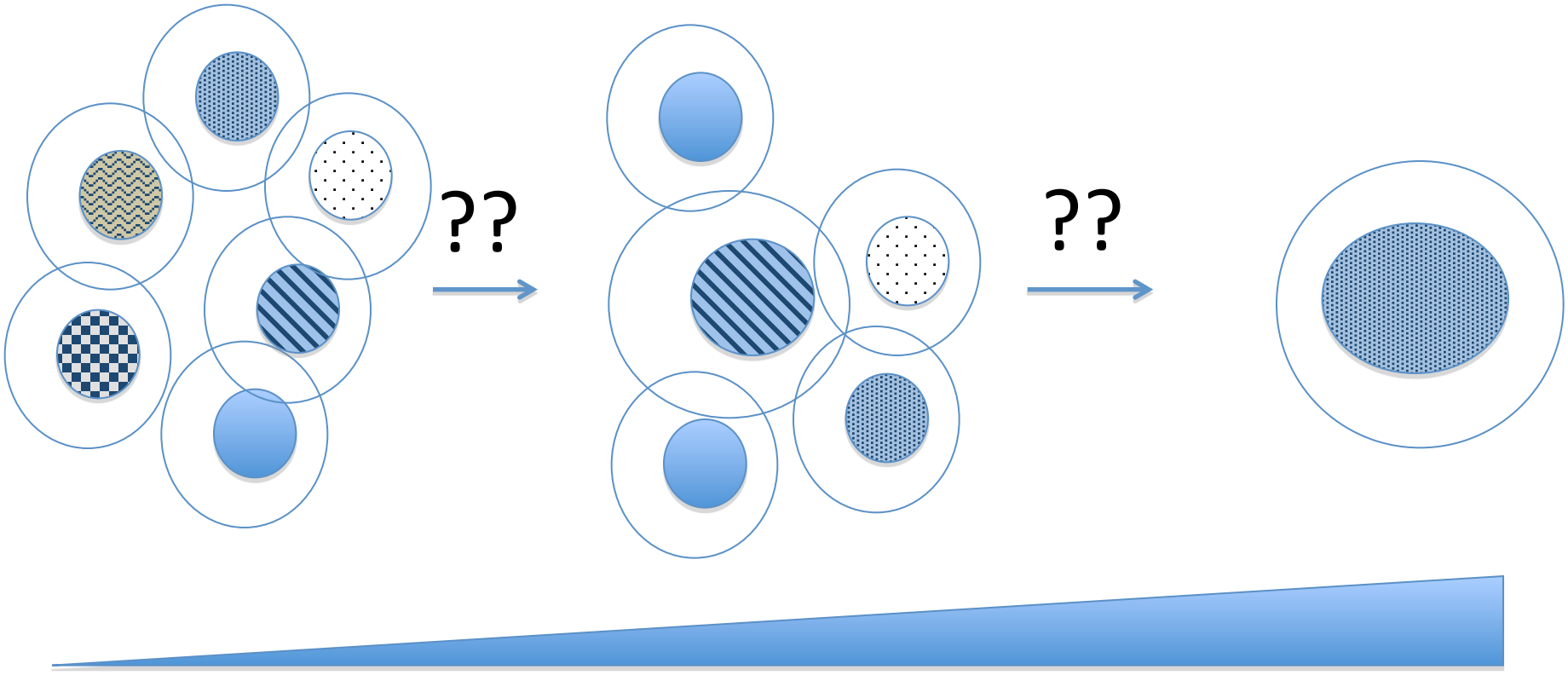
The forced expression of mut STAT3 favors Th17 differentiation of Naive T cells



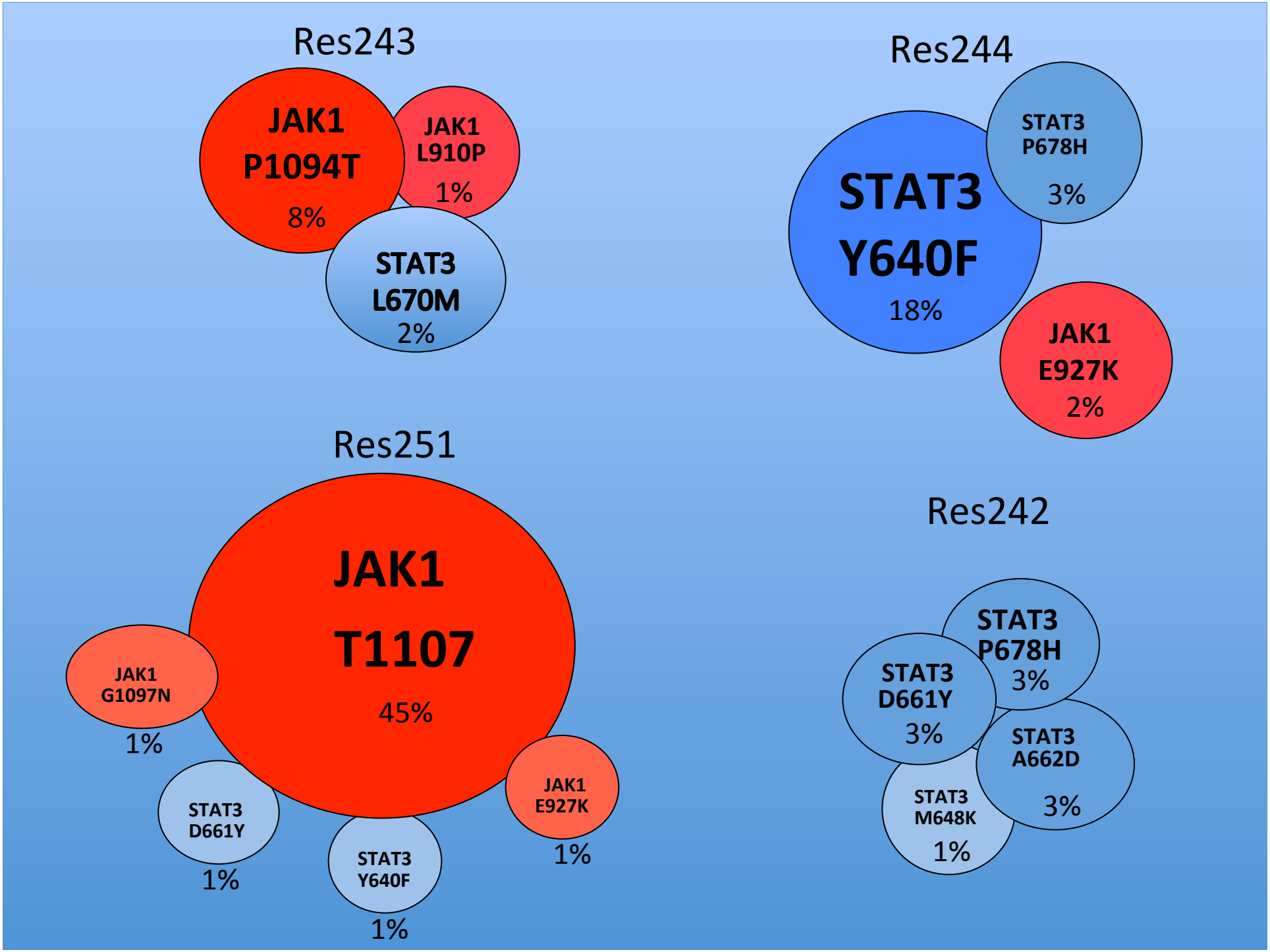
ALCL display a skewed expression of T-cell master regulators



Predicting clonal evolution CD30+ LPD



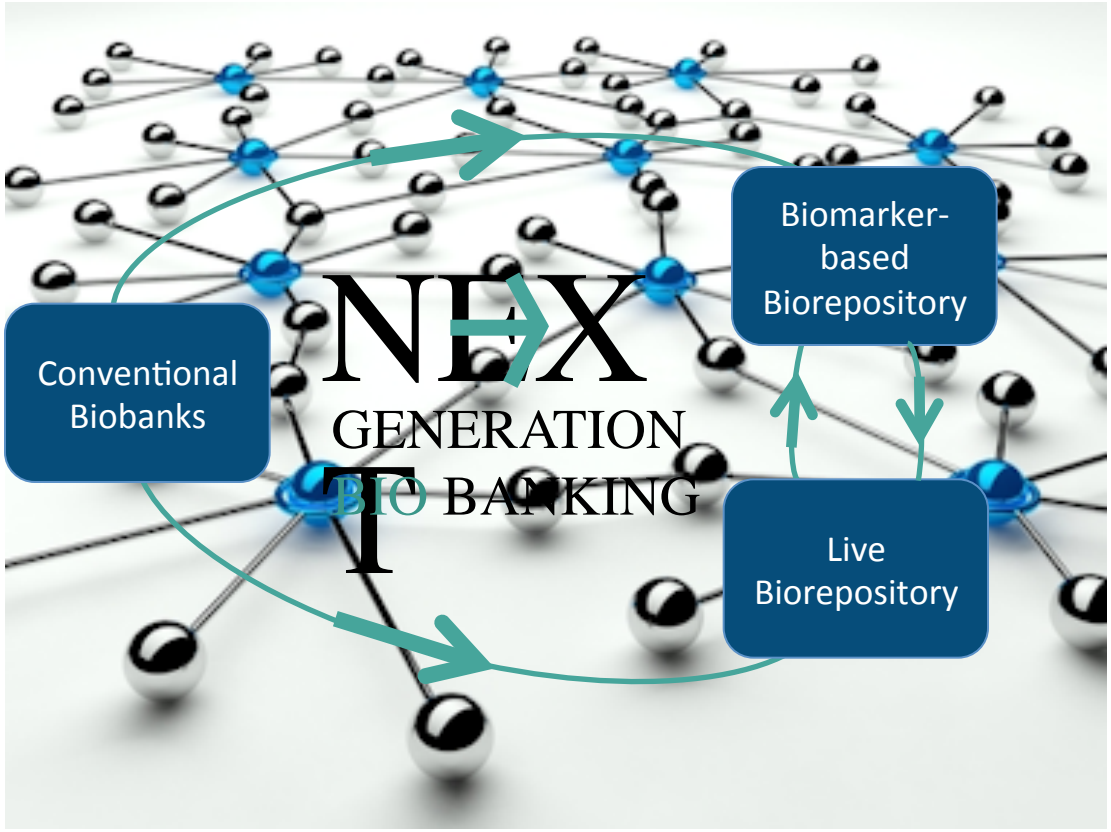
LyP A → C **cALCL** **Systemic cALCL**

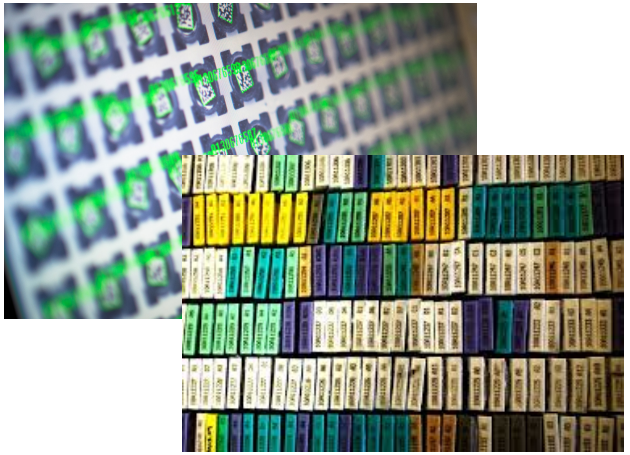

Res243
JAK1
P1094T
8%
JAK1
L910P
1%
STAT3
L670M
2%
Res244
STAT3
Y640F
18%
STAT3
P678H
3%
JAK1
E927K
2%
Res251
JAK1
T1107
45%
JAK1
G1097N
1%
STAT3
D661Y
1%
STAT3
Y640F
1%
JAK1
E927K
1%
Res242
STAT3
P678H
3%
STAT3
D661Y
3%
STAT3
A662D
3%
STAT3
M648K
1%

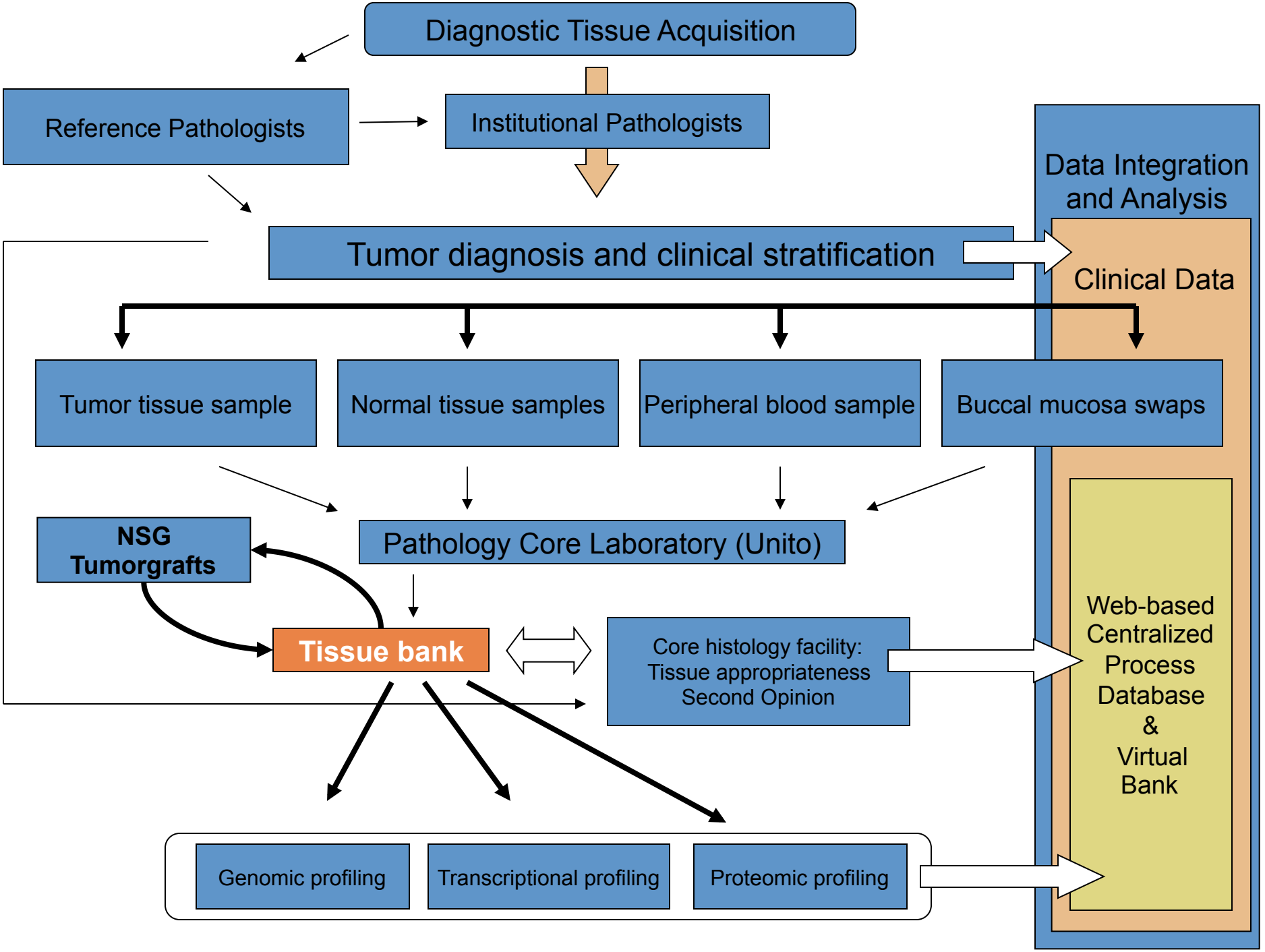

Tissue network
IRELAND
KINGDOM
Manchester
Liverpool
Birmingham
Cardiff
London
Amsterdam
NETH.
Rotterdam
Hamburg
Bremen
Berlin
Poznan
POLAND
Gdańsk
Łódź
Wroclaw
Celtic Sea
English Channel
Brussels
Lille
BEL.
Essen
Cologne
Bonn
GERMANY
Leipzig
Frankfurt am Main
Luxembourg
LUX.
Prague
CZECH REPUBLIC
Brno
Guernsey (U.K.)
Paris
Stuttgart
Strasbourg
Munich
Nantes
Vienna
Bratislava
LIECH.
AUSTRIA
Zürich
Bern
SWITZ.
Vaduz
Geneva
FRANCE
Bay of Biscay
MASSIF CENTRAL
Lyon
Milan
Nice
Ljubljana
Zagreb
Bordeaux
Bilbao
Toulouse
MONACO
Genoa
SAN MARINO
CROATIA
BOSNIA AND HERZEGOVINA
Sarajevo
Andorra la Vella
Marseille
Ligurian Sea
Florence
Porto
PYRENEES
ANDORRA
ITALY
Adriatic Sea
Zaragoza
Corsica
Rome
VATICAN CITY
PORTUGAL
Madrid
Barcelona
Naples
Lisbon
Tagus
Balearic Sea
SPAIN
Valencia
Sardinia
Tyrrhenian Sea
BALEARIC ISLANDS
Sevilla
Cagliari
Palermo
Gibraltar (U.K.)
Málaga
Mediterranean Sea
Strait of Gibraltar
Ceuta (SPAIN)
Alborán Sea
Algiers
Sicily
Melilla (SPAIN)
Oran
Tunis

Weill Cornell Medical College

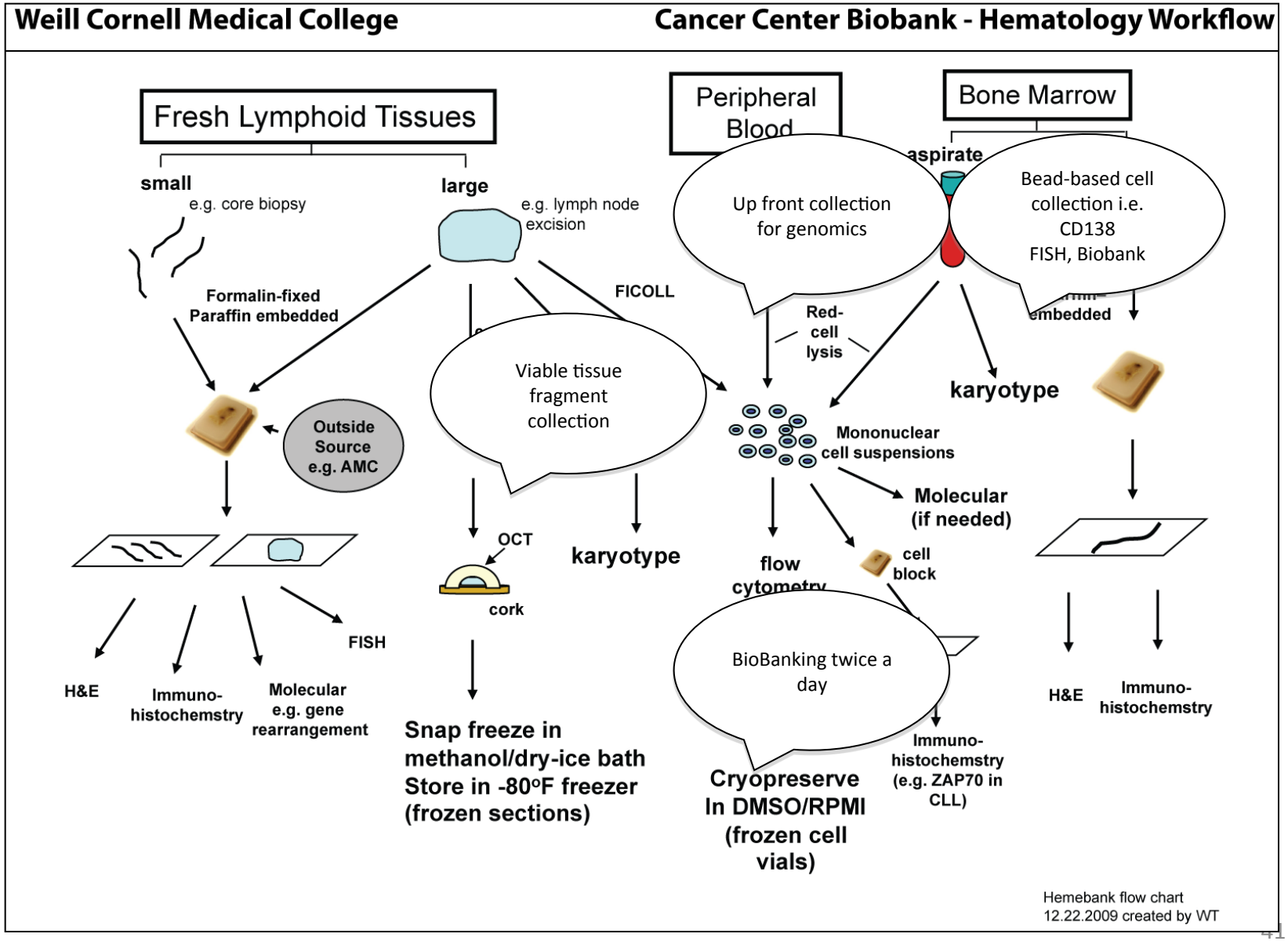
The Institutional Biobank at WCMC



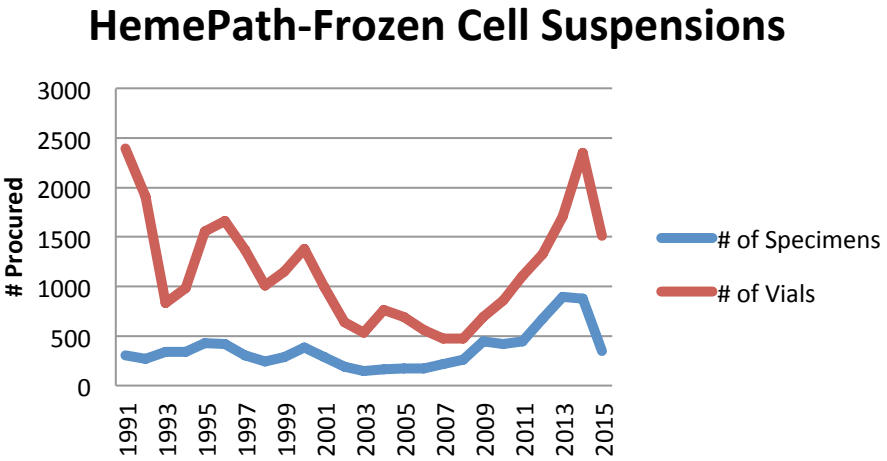



Diagnostic Tissue Acquisition
Reference Pathologists
Institutional Pathologists
Data Integration and Analysis
Tumor diagnosis and clinical stratification
Clinical Data
Tumor tissue sample
Normal tissue samples
Peripheral blood sample
Buccal mucosa swaps
NSG Tumorgrafts
Pathology Core Laboratory (Unito)
Tissue bank
Core histology facility:
Tissue appropriateness
Second Opinion
Web-based Centralized Process Database & Virtual Bank
Genomic profiling
Transcriptional profiling
Proteomic profiling

8.9 Example: HemPath Biopsy Specimen Collection

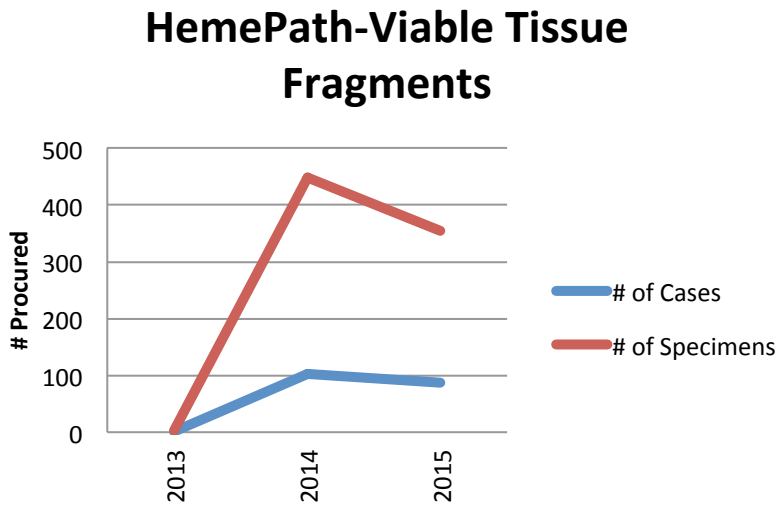


New trends in biobanking



Total Cell Suspensions

# of Cases	# of Specimens
8696	27435

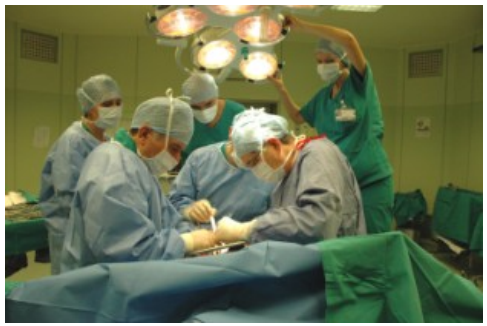


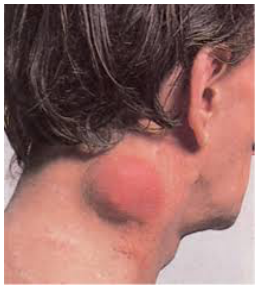
Total Viable Tissue Fragments

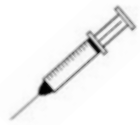
# of Cases	# of Specimens
104	451

Data update at 6/30/2015

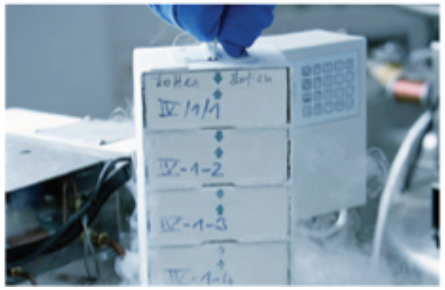
PDX and Precision Therapeutic Medicine



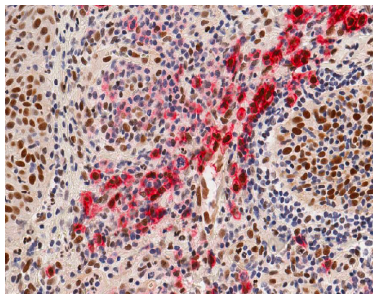




Biorepository



Molecular morphology

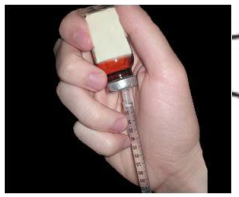


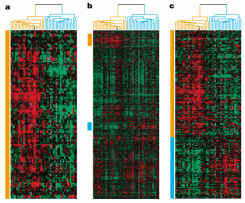
HTP molecular stratification

Tumor expansion

Preclinical "tailored" trials

Drug treatment





Molecular stratifiers

6

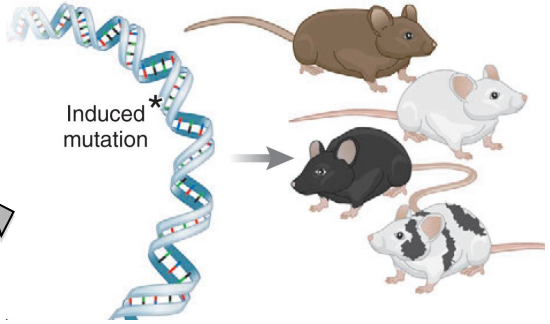
Results

Tumor growth inhibition results delivered to oncologist

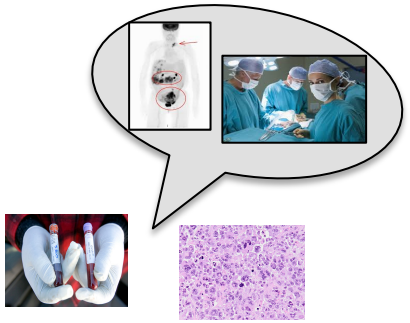
Experimental Therapeutics Program (ETP) @ WCMC

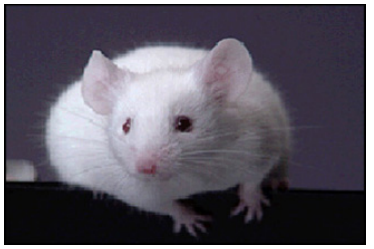
Zebra Fish Transgenes

Genetically engineered mice (GEM)

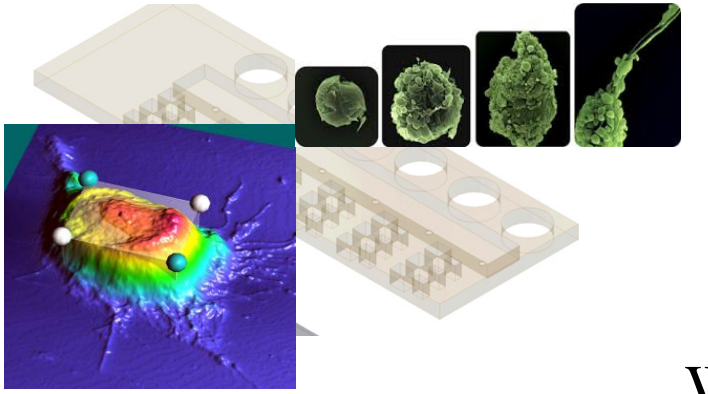


Patient Derived Tumorgrafts (PDT)





Micro-organoids



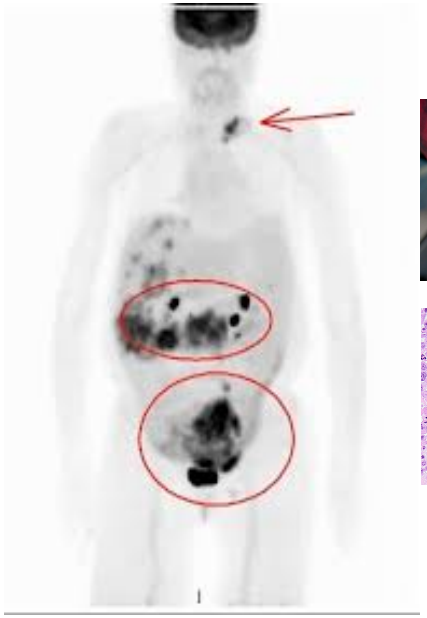
Spontaneous Lymphoma models

WCMC -Cornell Ithaca

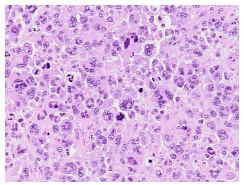
Why we need reproducible lymphoma PDX?

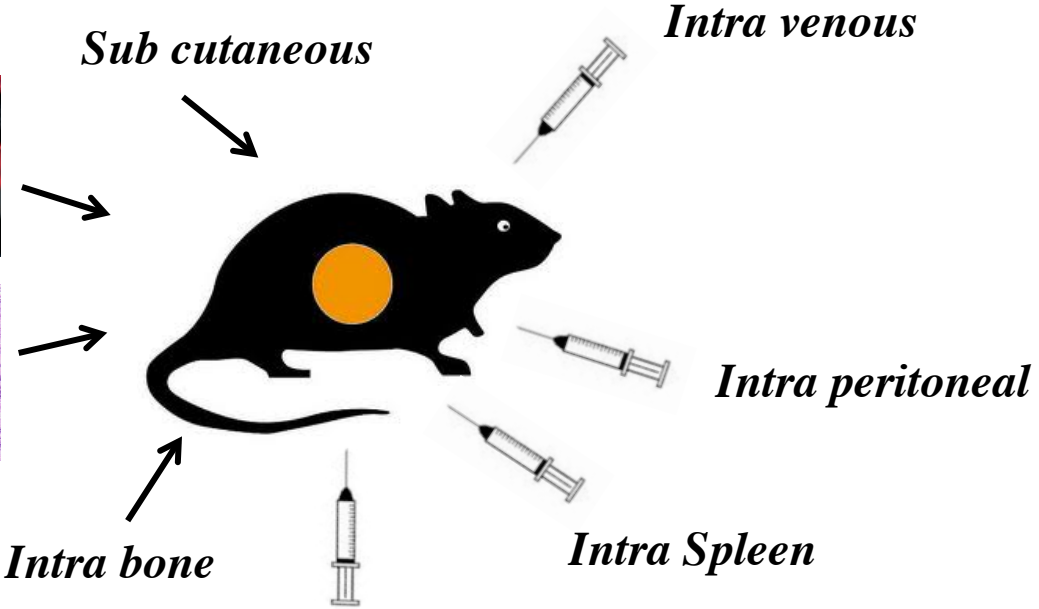
- Although many lymphoid cell lines exist, various lymphoma subtypes lack authentic in vitro models i.e. CLL, HCL, FCCL, PTCL-NOS, etc.
- Spontaneous lymphoma models are rare and current transgenic mice are driven by constitutive oncogenes and lack the complex genomic heterogeneity of human cancers.
- GEM and/or xenografts partly predict the clinic responses seen in clinical settings.
- No representative refractory lymphoma models exist.
- Fully humanized models are needed, i.e. immunotherapies, host-lymphoma interactions.
- Regardless of a considerably progress the over survival of lymphoma patients remains modest.

How critical are the implantation routes in lymphoma PDX grafting?

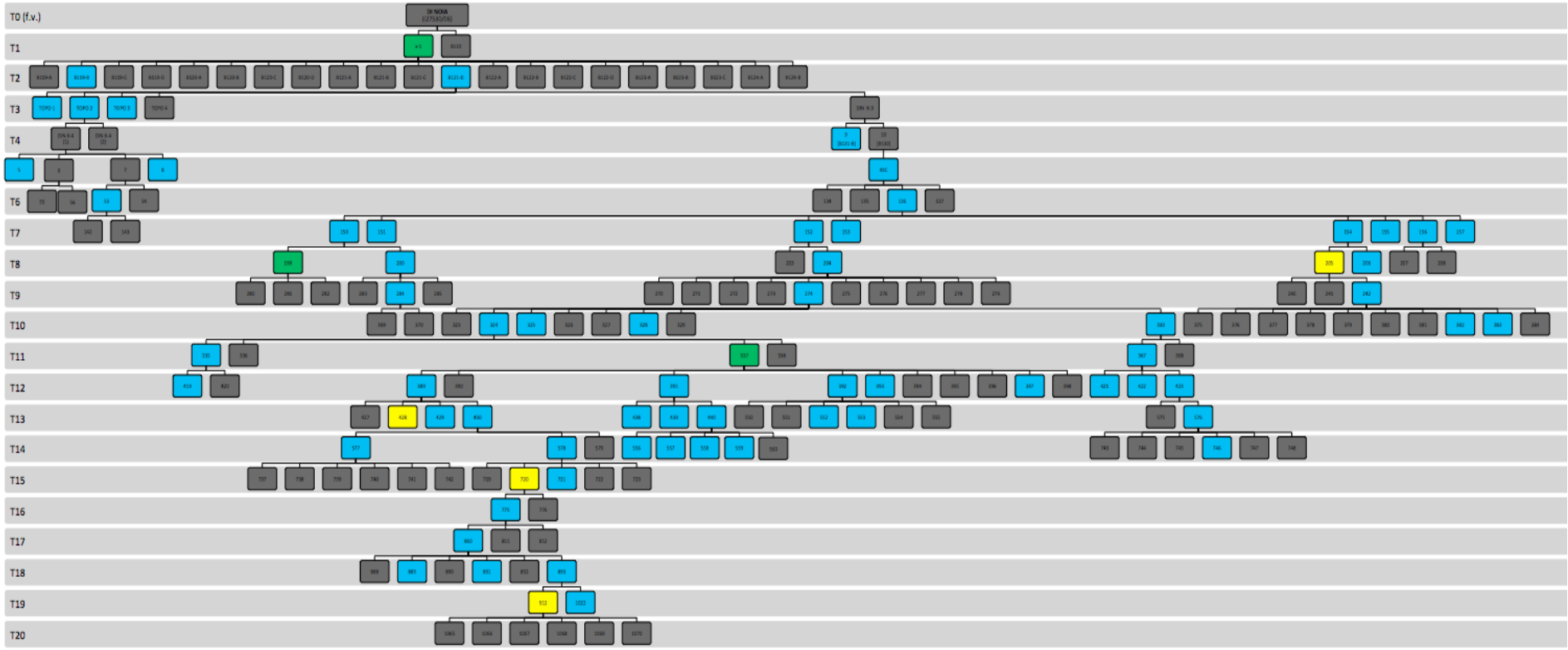


Diagnostic sample



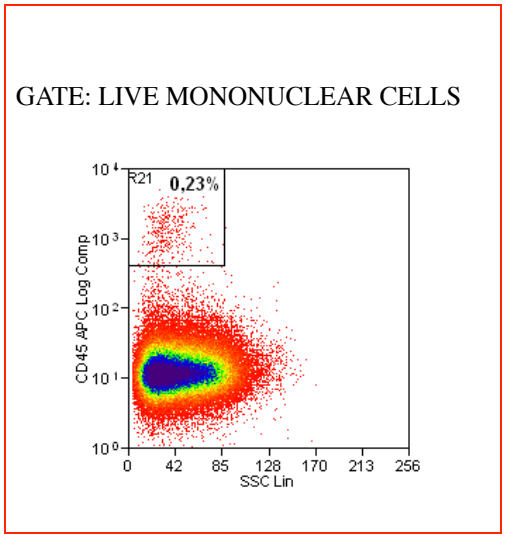


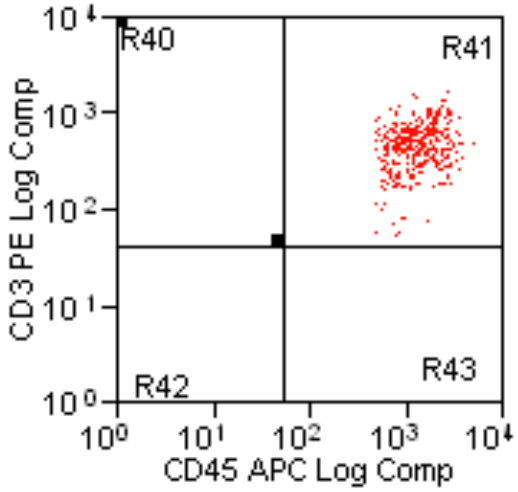
Temporal propagation of PDX lymphomas

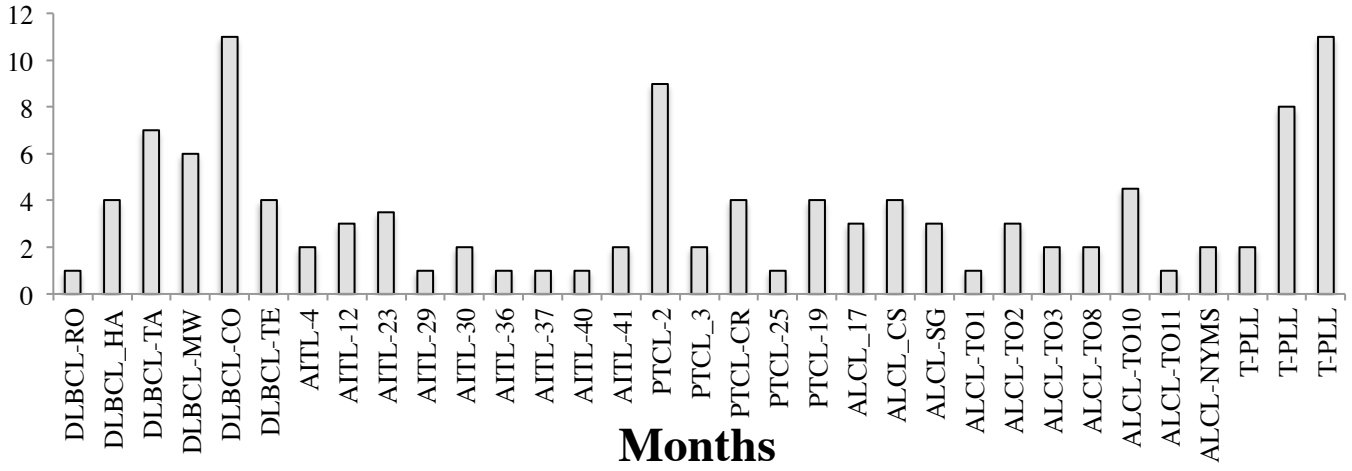


ALCL-1

Graft versus host represents a fatal hurdle in the generation of PDX lymphoma.



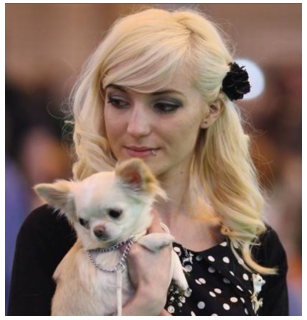
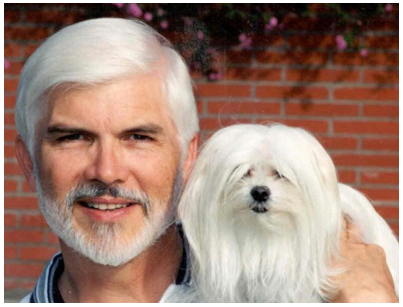




Do PDTX fully recapitulate their corresponding primary lesions





PDX Flow data: Discovery and therapeutics

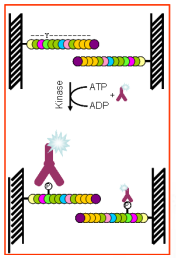
Targeted screening

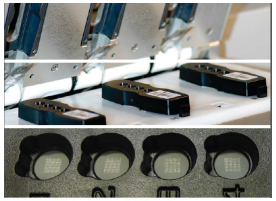
Treatments

No ***Yes***

Drug development

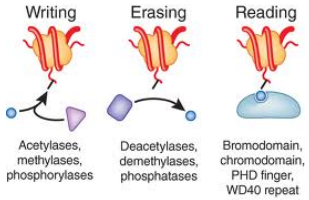
Real time Kinome Drug fitness



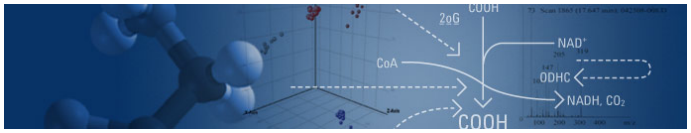


NGS and deep sequencing

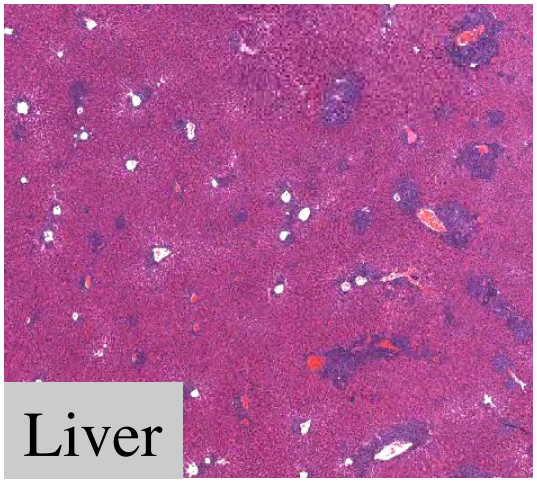
DNA regulation

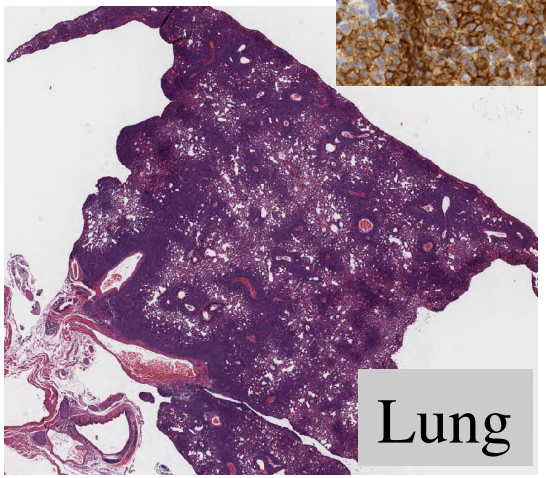


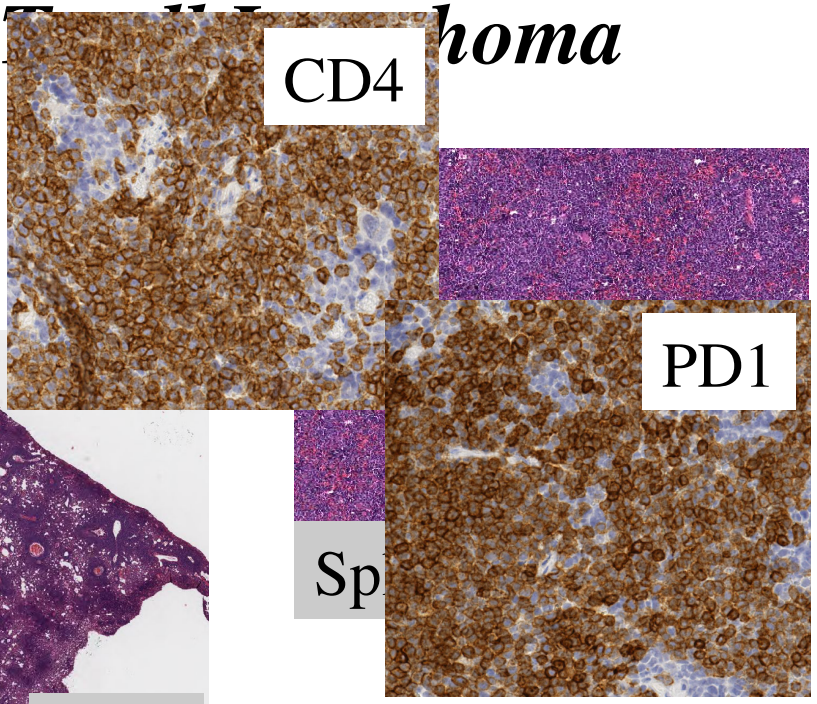
Biomarkers: metabolomics and peptidomics

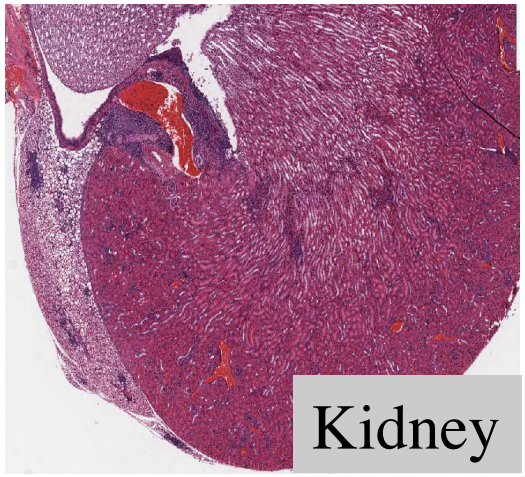


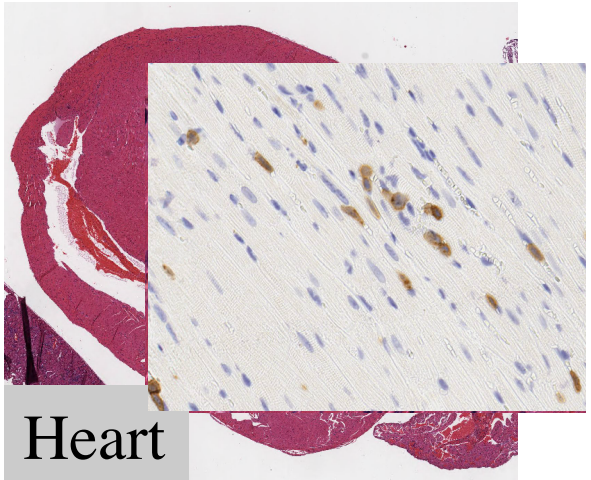
MSKCC-WCMC-6 (T2)
Angioimmunoblastic T-cell lymphoma



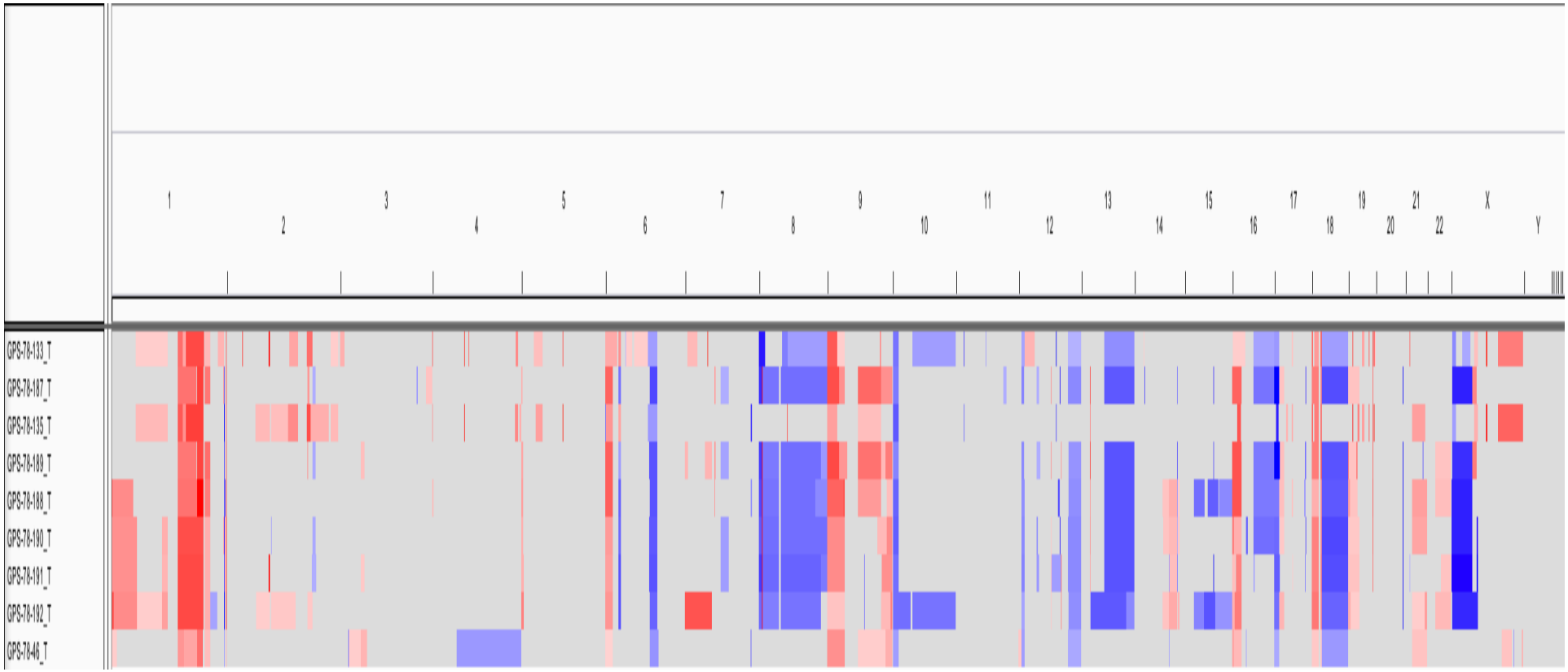




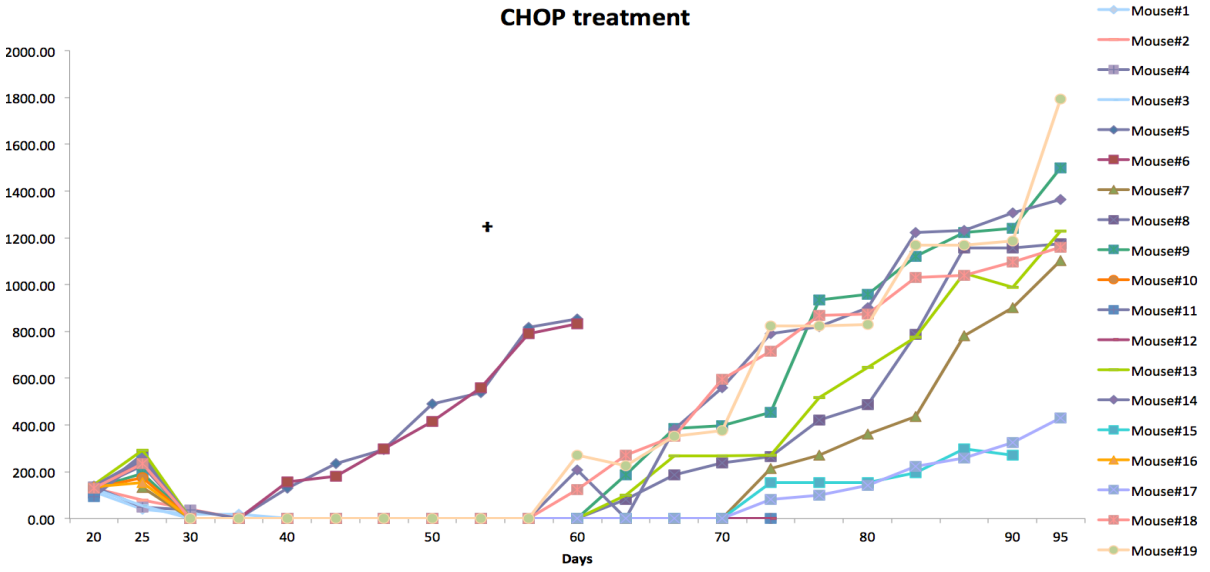


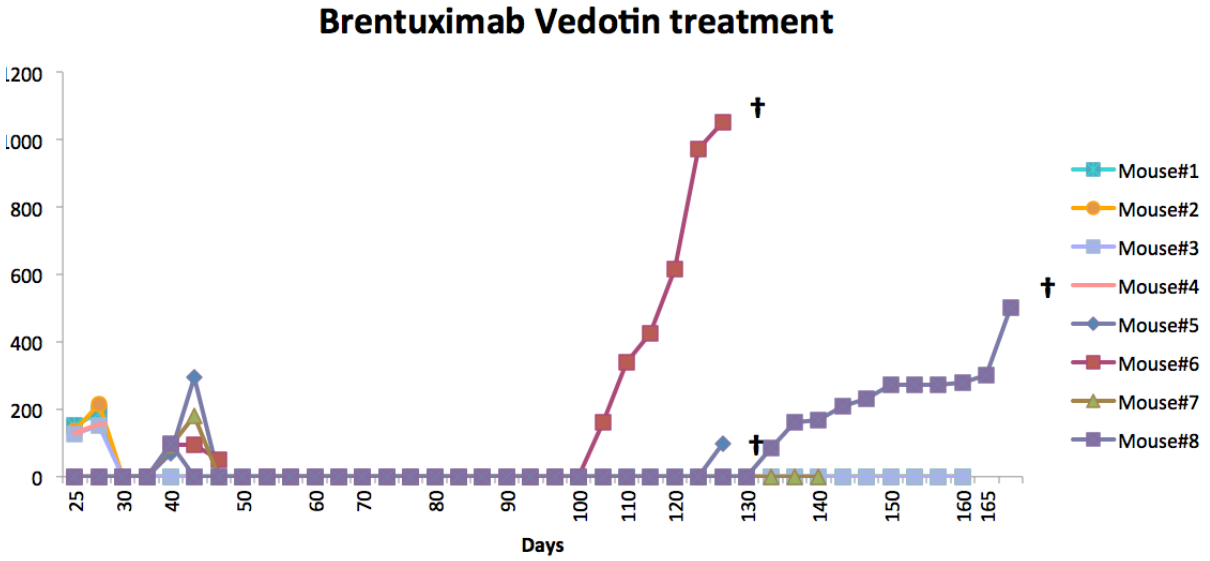


SNP array identify analogous patient genomic defects in primary and corresponding PDTX



Genomic and biological characterization of cALCL PDTX





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The European T-cell Lymphoma Study Group

Genetics-driven targeted management of lymphoid malignancies

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