INSTITUTE OF APPLIED BIOSCIENCES
ΙΝΣΤΙΤΟΥΤΟ ΕΦΑΡΜΟΣΜΕΝΩΝ ΒΙΟΕΠΙΣΤΗΜΩΝ
CERTH

Dissecting CLL Immunogenetics and Emerging B Cell Receptor Stereotypes

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Disclosures

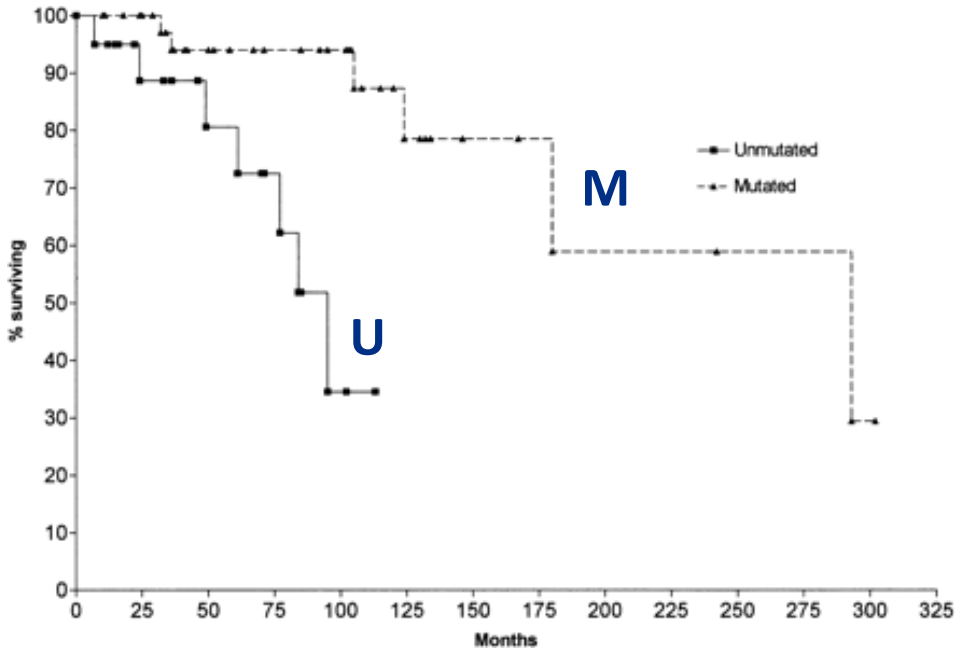
Janssen – research funding, honoraria

Abbvie – research funding, honoraria

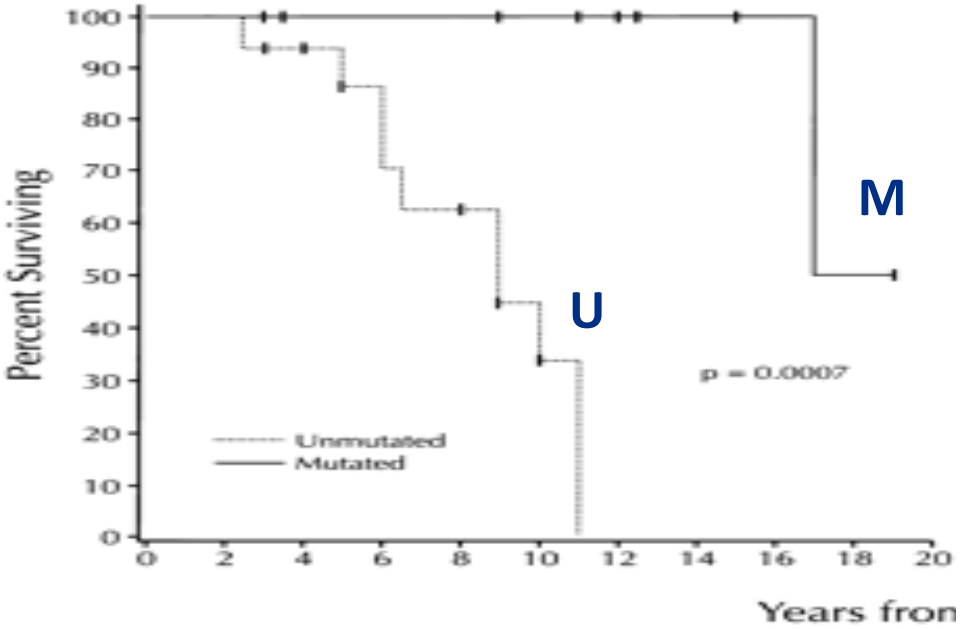
Gilead Sciences – research funding, honoraria

20th anniversary

CLL: better with mutated IG receptors



Hamblin et al, Blood 1999



Damle et al., Blood 1999

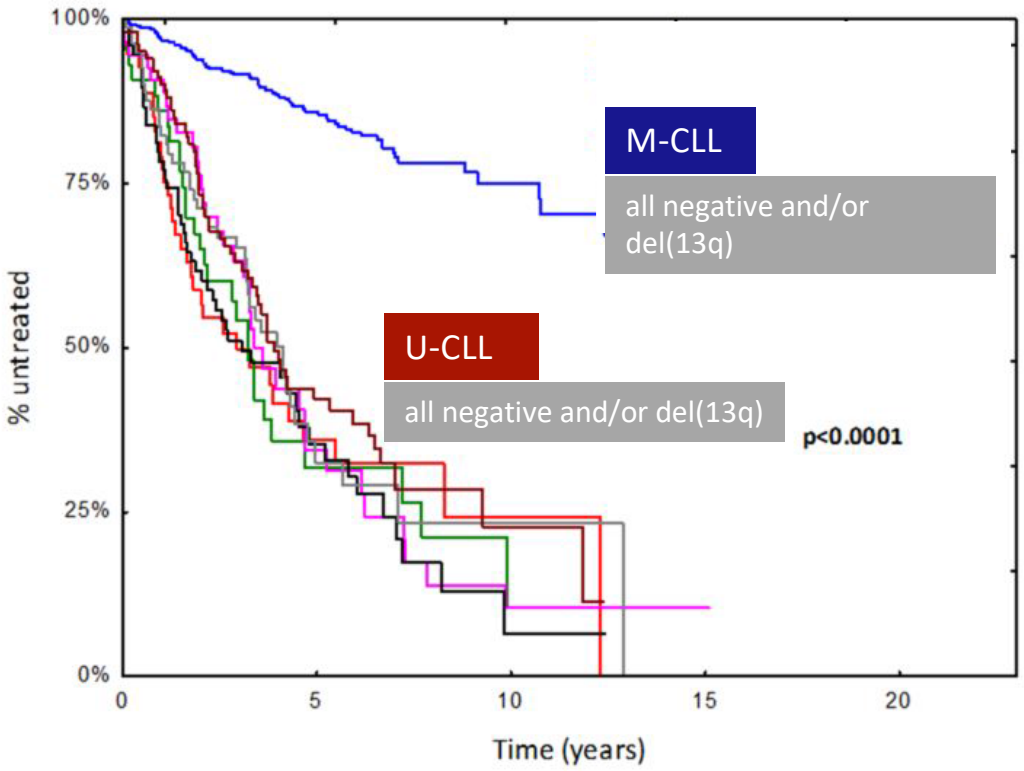
immunogenetics in context

in the context of?

genomic aberrations

TP53, NOTCH1, SF3B1 mutations

del(11q), del(13q), del(17p), +12



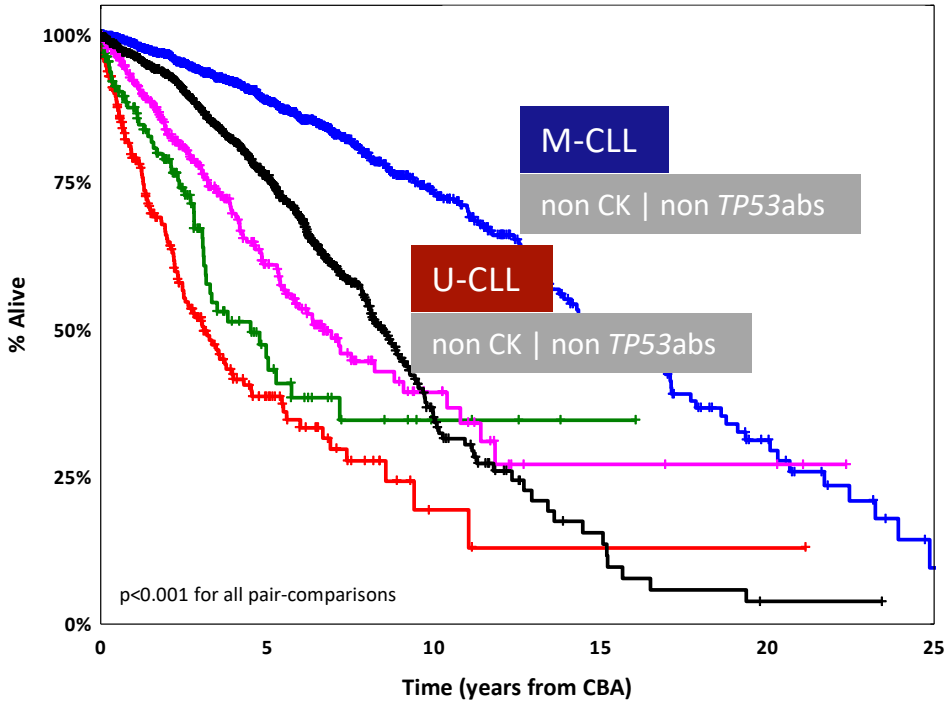
Baliakas et al. Leukemia 2015

in the context of?

genomic aberrations

TP53 mutations

complex karyotype



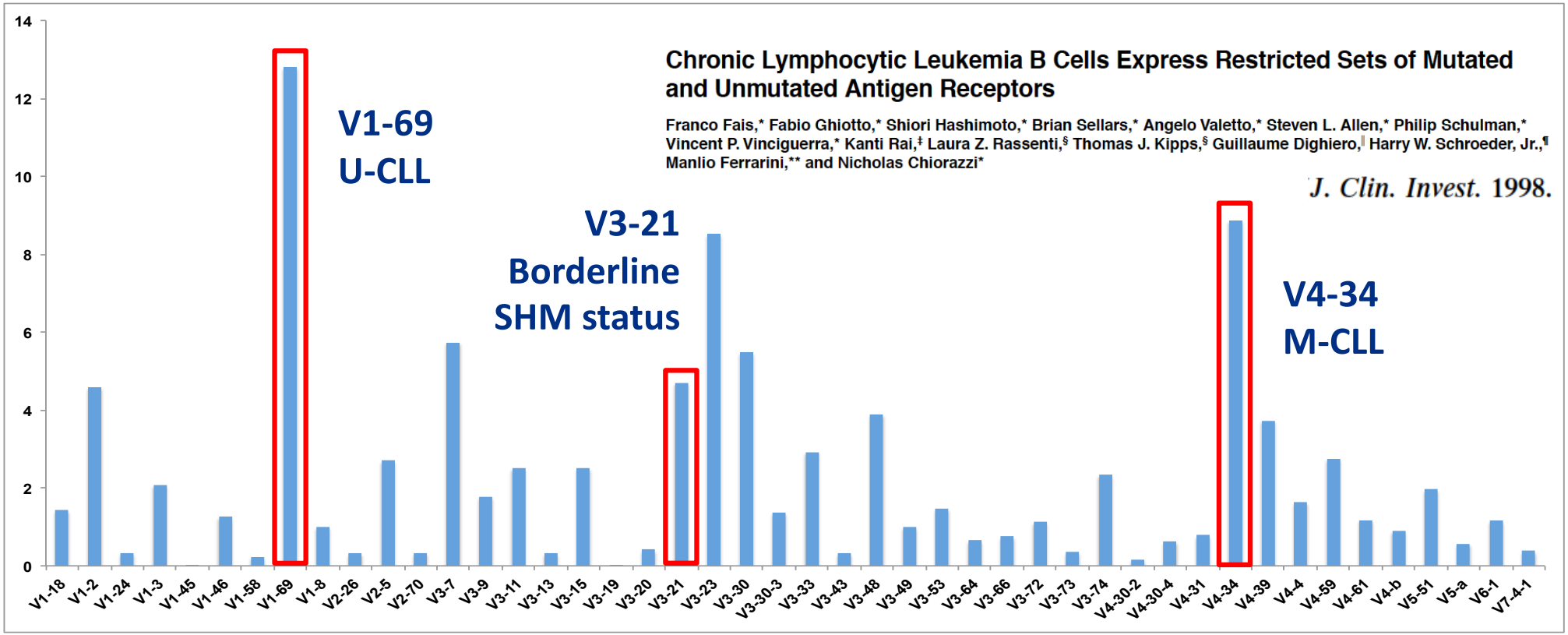
U-CLL: unmutated IG; M-CLL: mutated IG
CK: complex karyotype; *TP53*abs: del(17p) and/or *TP53* mutation

Baliakas et al. Blood 2019

BcR IG
the ultimate driver?

why?

CLL clones express a restricted IG gene repertoire



Fais et al. J Clin Invest 1998; Murray et al. Blood 2008; Agathangelidis et al. Blood 2012

Chronic lymphocytic leukemias utilizing the V_H3-21 gene display highly restricted V_λ2-14 gene use and homologous CDR3s: implicating recognition of a common antigen epitope

Gerard Tobin, Ulf Thunberg, Anna Johnson, Inger Eriksson, Ola Söderberg, Karin Karlsson, Mats Merup, Gunnar Juliusson, Juhani Vilpo, Gunilla Enblad, Christer Sundström, Göran Roos, and Richard Rosenquist

BLOOD, 15 JUNE 2003 • VOLUME 101

Multiple Distinct Sets of Stereotyped Antigen Receptors Indicate a Role for Antigen in Promoting Chronic Lymphocytic Leukemia

Bradley T. Messmer,[1] Emilia Albesiano,[1] Dimitar G. Efremov,[4] Fabio Ghiotto,[2,3,4] Steven L. Allen,[1,2] Jonathan Kolitz,[1,2] Robin Foa,[8] Rajendra N. Damle,[1,2] Franco Fais,[5] Davorka Messmer,[1] Kanti R. Rai,[1,9,10] Manlio Ferrarini,[6,7] and Nicholas Chiorazzi[1,2]

J. Exp. Med. © The Rockefeller University
Volume 200, Number 4, August 16, 2004

~50% of IGHV3-21 CLL carry (quasi)identical BcR IG

stereotyped

repeated with limited or no variation

probability that ***two different B cell*** clones carry identical BcR IG

$$\mathbf{1:10^{-12}}$$

CLL is not an unfortunate stroke of serendipity

antigen selection

in CLL ontogeny

BcR IG stereotypes in CLL

frequency?

relation to somatic hypermutation status?

distinctive features?

implications for disease pathogenesis?

clinical significance?

2012

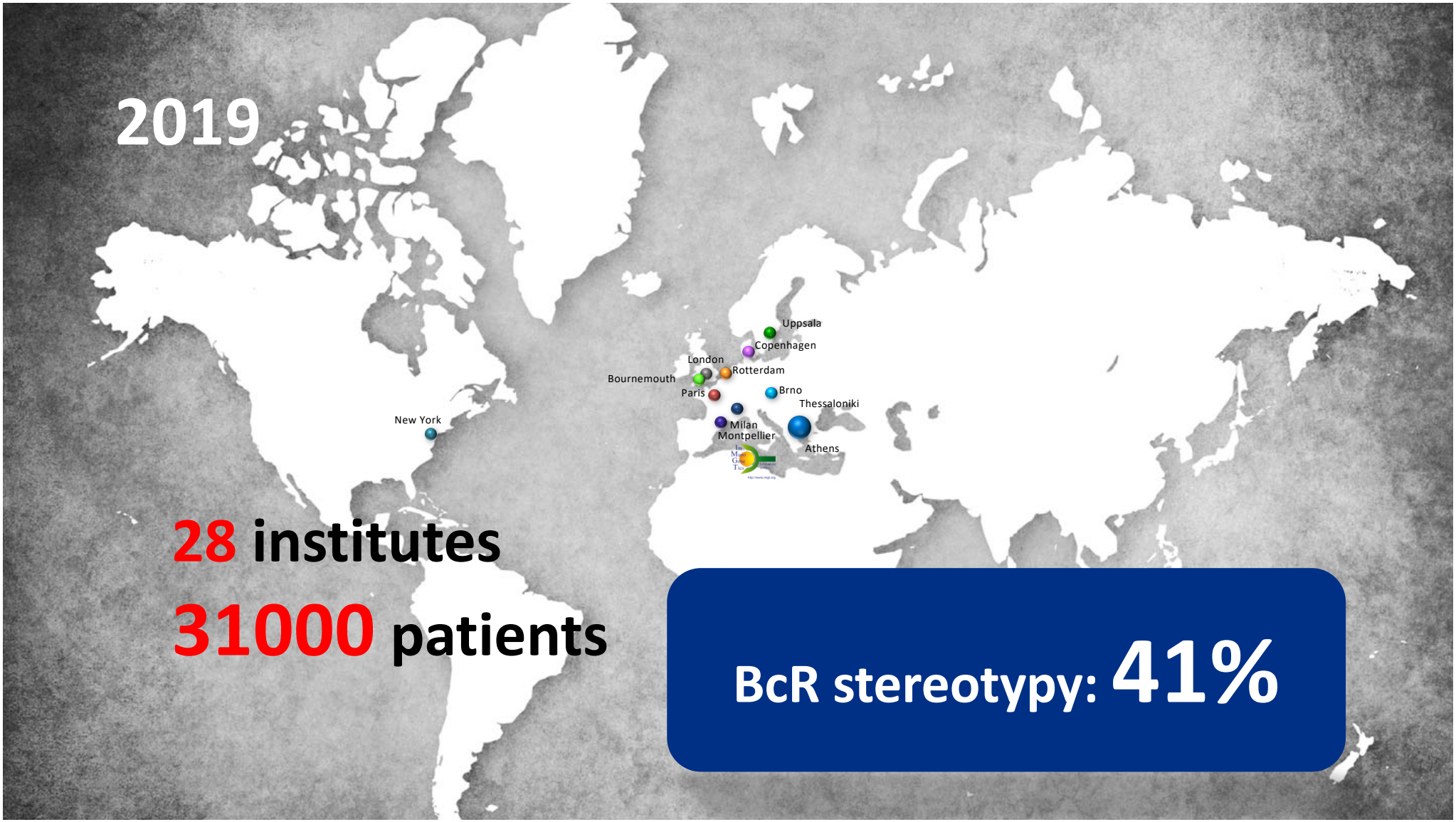
Stereotyped B-cell receptors in one-third of chronic lymphocytic leukemia: a molecular classification with implications for targeted therapies

Andreas Agathangelidis,[1] Nikos Darzentas,[1] Anastasia Hadzidimitriou,[1] Xavier Brochet,[2] Fiona Murray,[3] Xiao-Jie Yan,[4] Zadie Davis,[5] Ellen J. van Gastel-Mol,[6] Cristina Tresoldi,[7] Charles C. Chu,[4] Nicola Cahill,[8] Veronique Giudicelli,[2] Boris Tichy,[9] Lone Bredo Pedersen,[10] Letizia Foroni,[11] Lisa Bonello,[12] Agnieszka Janus,[13] Karin Smedby,[14] Achilles Anagnostopoulos,[15] Helene Merle-Beral,[16] Nikolaos Laoutaris,[17] Gunnar Juliusson,[18] Paola Francia di Celle,[12] Sarka Pospisilova,[9] Jesper Jurlander,[10] Christian Geisler,[10] Athanasios Tsaftaris,[1] Marie-Paule Lefranc,[2] Anton W. Langerak,[6] David Graham Oscier,[5] Nicholas Chiorazzi,[4] Chrysoula Belessi,[17] Frederic Davi,[16] Richard Rosenquist,[8] Paolo Ghia,[13] and Kostas Stamatopoulos[1,15]

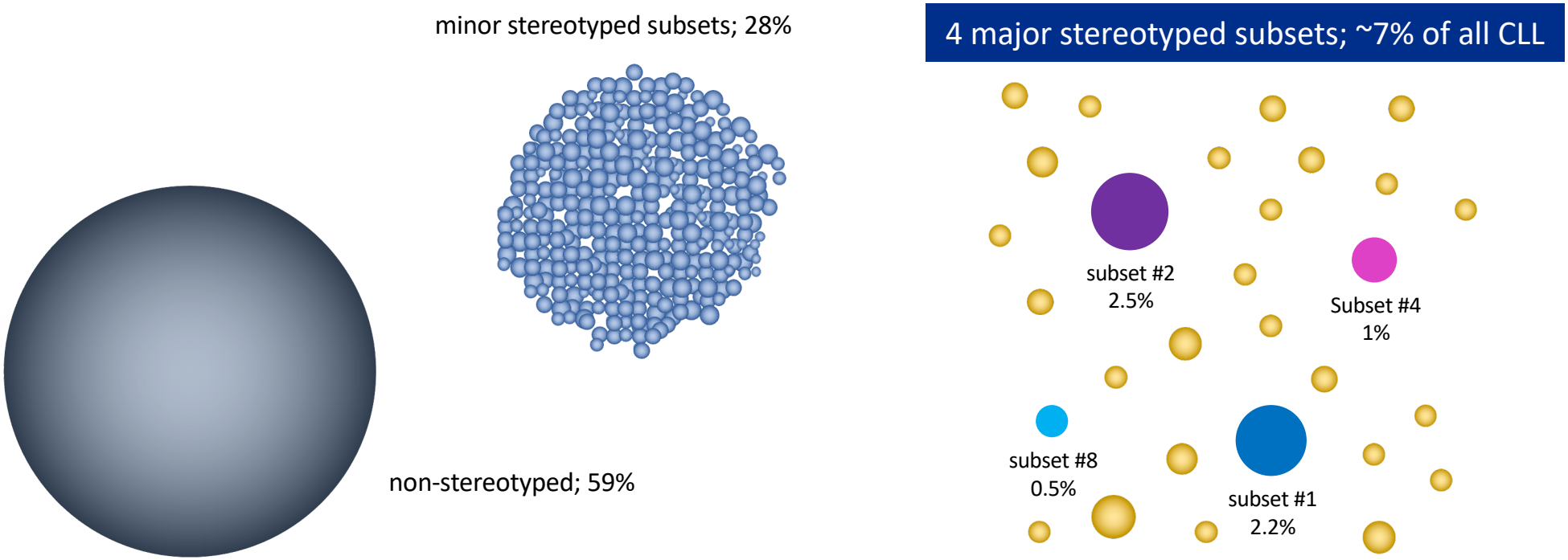
11 institutions

7424 patients

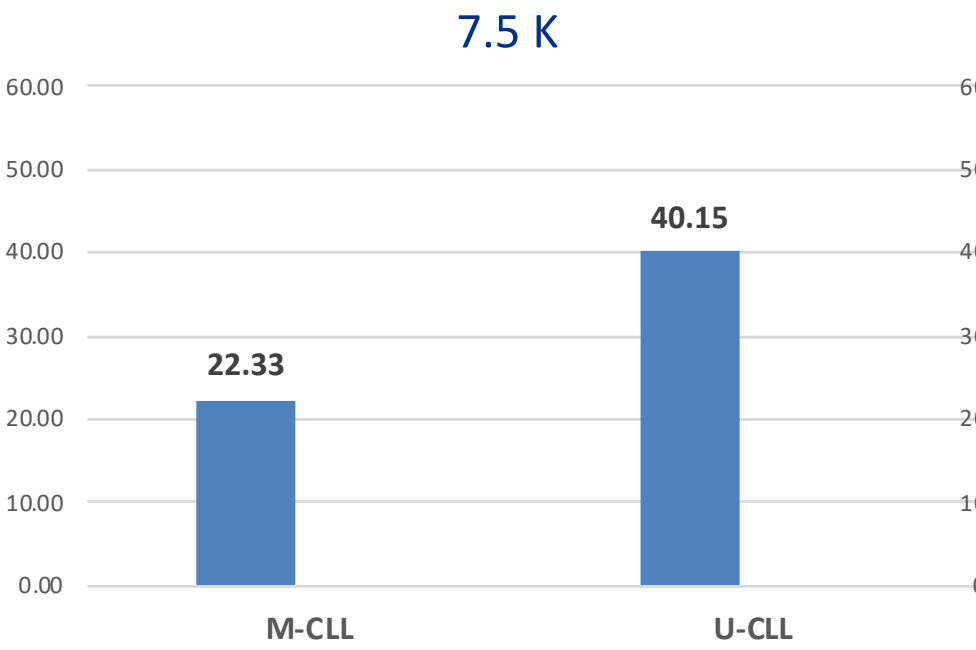
BcR stereotypy: 33%
‘major’ subsets


2019
Uppsala
Copenhagen
London
Rotterdam
Bournemouth
Paris
Brno
Thessaloniki
New York
Milan
Montpellier
Athens
28 institutes
31000 patients
BcR stereotypy: 41%

few stereotyped subsets account for a sizeable fraction of all CLL

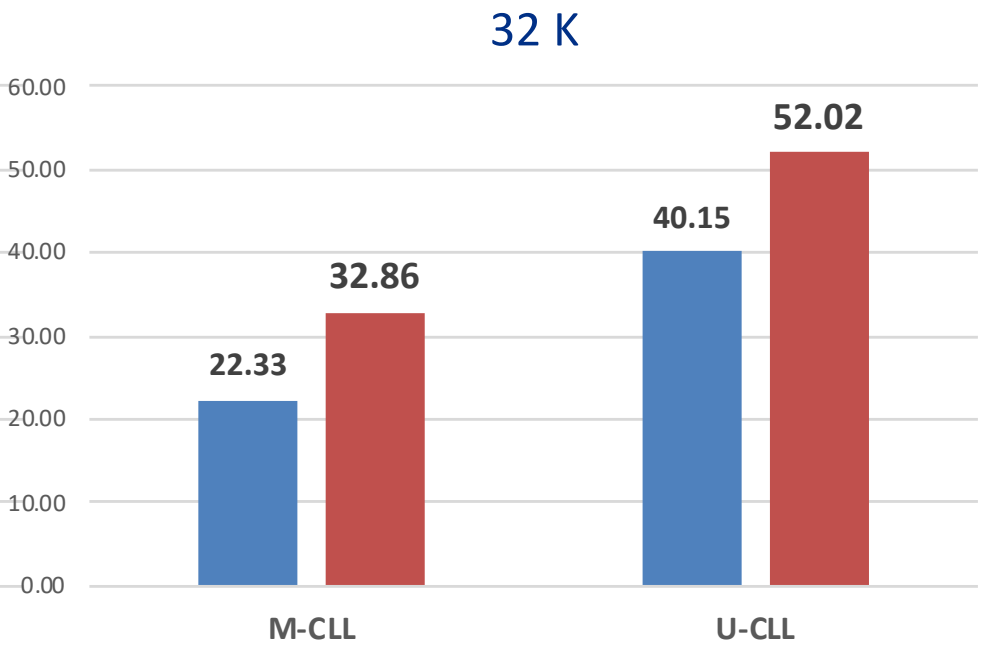


stereotypy is more frequent in U-CLL



Agathangelidis et al. Blood 2012

stereotypy is not infrequent in M-CLL



Agathangelidis et al. in preparation

speculation

with a relevant increase in numbers, perhaps all CLL may turn out stereotyped

question

did we previously miss stereotypes in M-CLL?

M-CLL subsets often carry degenerate motifs

subset #63

IGHD gene	%
IGHD1-1*01 F	7,69
IGHD1-14*01 ORF	11,54
IGHD1-7*01 F	3,85
IGHD2-15*01 F	7,69
IGHD2-2*02 F	3,85
IGHD2-21*02 F	3,85
IGHD2-8*01 F	3,85
IGHD3-10*01 F	3,85
IGHD4-11*01 ORF	3,85
IGHD4-17*01 F	7,69
IGHD4-23*01 ORF	11,54
IGHD5-18*01 F	3,85
IGHD6-19*01 F	7,69
IGHD6-25*01 F	3,85
IGHD6-6*01 F	3,85
IGHD7-27*01 F	11,54

IGHJ gene	%
IGHJ1*01 F	15,38
IGHJ3*02 F	3,85
IGHJ4*02 F	26,92
IGHJ5*01 F	42,31
IGHJ6*02 F	11,54

Agathangelidis et al. in preparation

M-CLL subsets often carry degenerate motifs

subset #123

IGHD gene	%
IGHD1-1*01 F	10,81
IGHD1-14*01 ORF	2,70
IGHD1-26*01 F	2,70
IGHD1-7*01 F	2,70
IGHD2-2*01 F	5,41
IGHD2-8*01 F	2,70
IGHD3-16*02 F	5,41
IGHD4-17*01 F	10,81
IGHD4-23*01 ORF	5,41
IGHD5-12*01 F	5,41
IGHD5-18*01 F	13,51
IGHD5-24*01 ORF	5,41
IGHD6-19*01 F	2,70
IGHD6-25*01 F	2,70
IGHD6-6*01 F	2,70
IGHD7-27*01 F	18,92

IGHJ gene	%
IGHJ1*01 F	16,33
IGHJ4*02 F	42,86
IGHJ5*01 F	38,78
IGHJ6*02 F	2,04

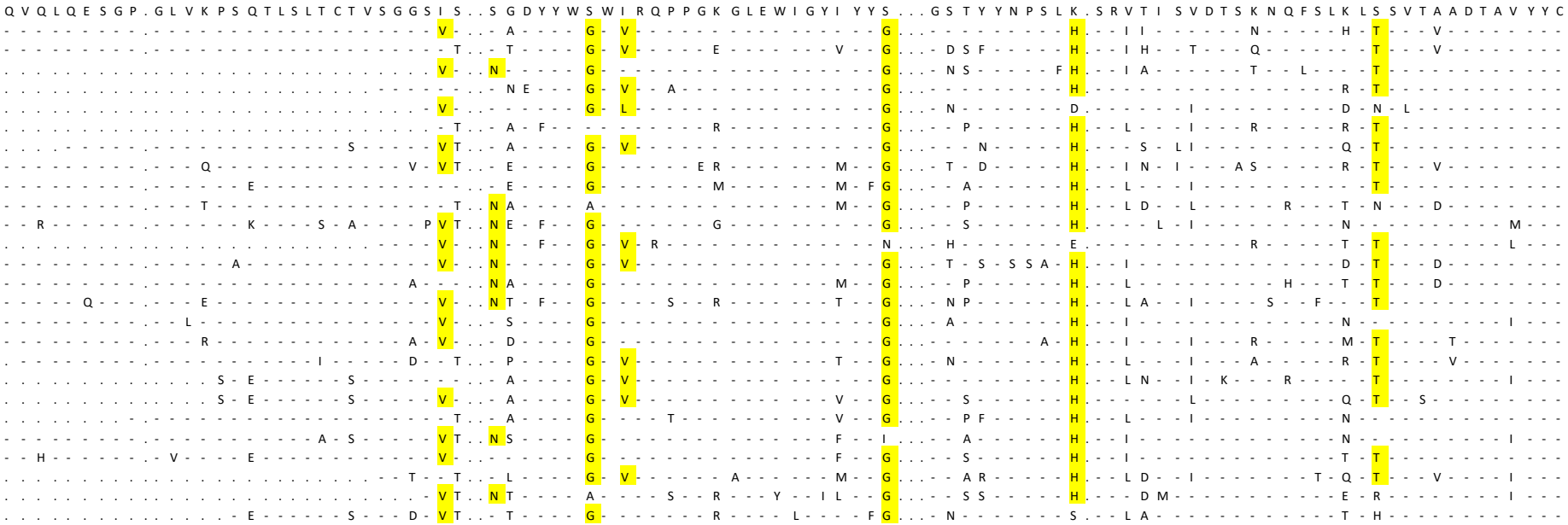
Agathangelidis et al. in preparation

is there additional proof that they are truly stereotyped?

compelling evidence for

stereotyped SHM

subset #63

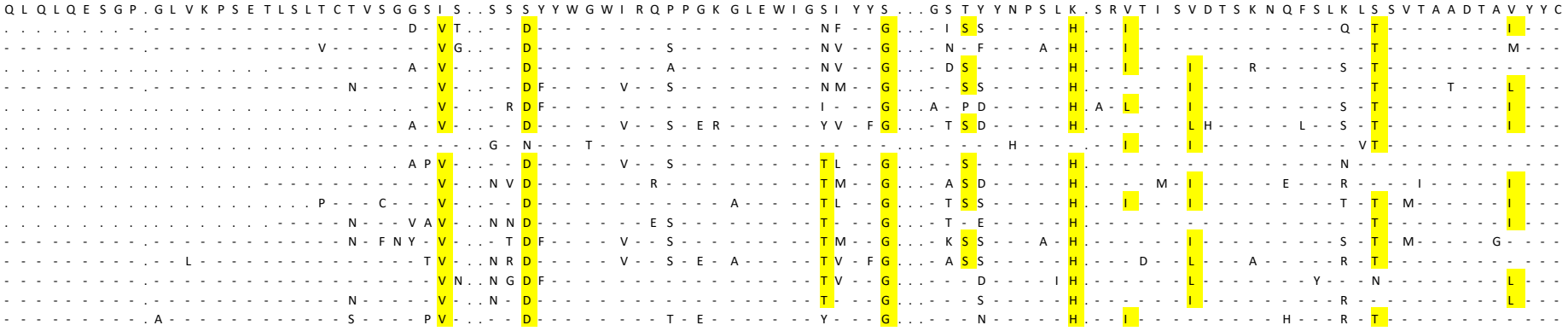


Agathangelidis et al. in preparation

compelling evidence for

stereotyped SHM

subset #123



Agathangelidis et al. in preparation

compelling evidence for

intra-subset heterogeneity reflected intraclonally

subset #4

VH CDR3s of
265 different cases
Sanger data

patient 1

patient 2

patient 3

VH CDR3s of hundreds of subclones of
individual cases
NGS data

Gemenetzi et al. iwCLL 2019

stereotyped subsets can appear very similar

subset #7A1
VH CDR3 length: 22 amino acids

subset #7A2
VH CDR3 length: 22 amino acids

subset #N23-1-2
VH CDR3 length: 22 amino acids

subset #7B2
VH CDR3 length: 23 amino acids

subset #V1-2/23-1
VH CDR3 length: 23 amino acids

subset #7D2
VH CDR3 length: 25 amino acids

U-CLL

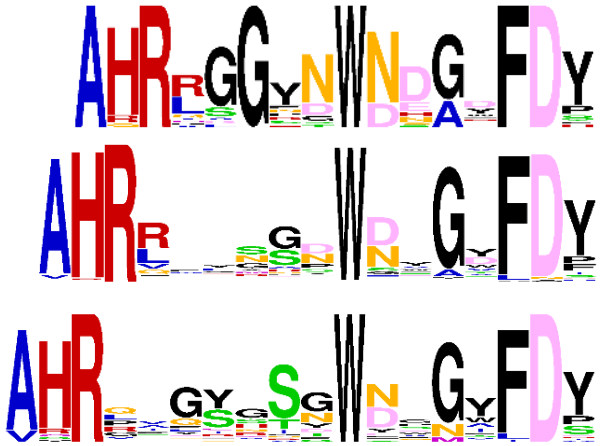
Agathangelidis et al. in preparation

stereotyped subsets can appear very similar

subset #148A
VH CDR3 length: 16 amino acids

subset #148B
VH CDR3 length: 17 amino acids

subset #148C
VH CDR3 length: 18 amino acids



M-CLL

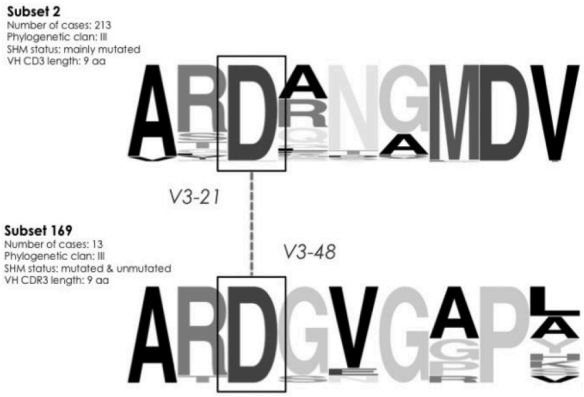
Agathangelidis et al. in preparation

new concept

satellite subsets

the instructive case of subsets #2 and #169

9/acidic-3 VH CDR3



	Subset #2	**Subset #169**	
relative frequency	~3%	~0.2%	
IGHV gene	IGHV3-21	IGHV3-48	97% identical
Light chain	IGLV3-21	IGLV3-21	

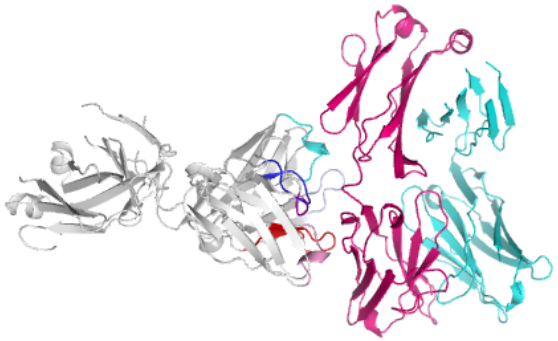
Murray et al. Blood 2008; Hadzidimitriou et al. Blood 2009; Darzentas et al. Leukemia 2010; Agathangelidis et al. Blood 2012; Minici et al. Nat Commun 2017

Distinct homotypic B-cell receptor interactions shape the outcome of chronic lymphocytic leukaemia

Claudia Minici[1,2,*], Maria Gounari[3,*,†], Rudolf Übelhart[4], Lydia Scarfò[2,3,5], Marcus Dühren-von Minden[4], Dunja Schneider[6], Alpaslan Tasdogan[4], Alabbas Alkhatib[6], Andreas Agathangelidis[3], Stavroula Ntoufa[7], Nicholas Chiorazzi[8], Hassan Jumaa[4], Kostas Stamatopoulos[7,9], Paolo Ghia[2,3,5] & Massimo Degano[1]

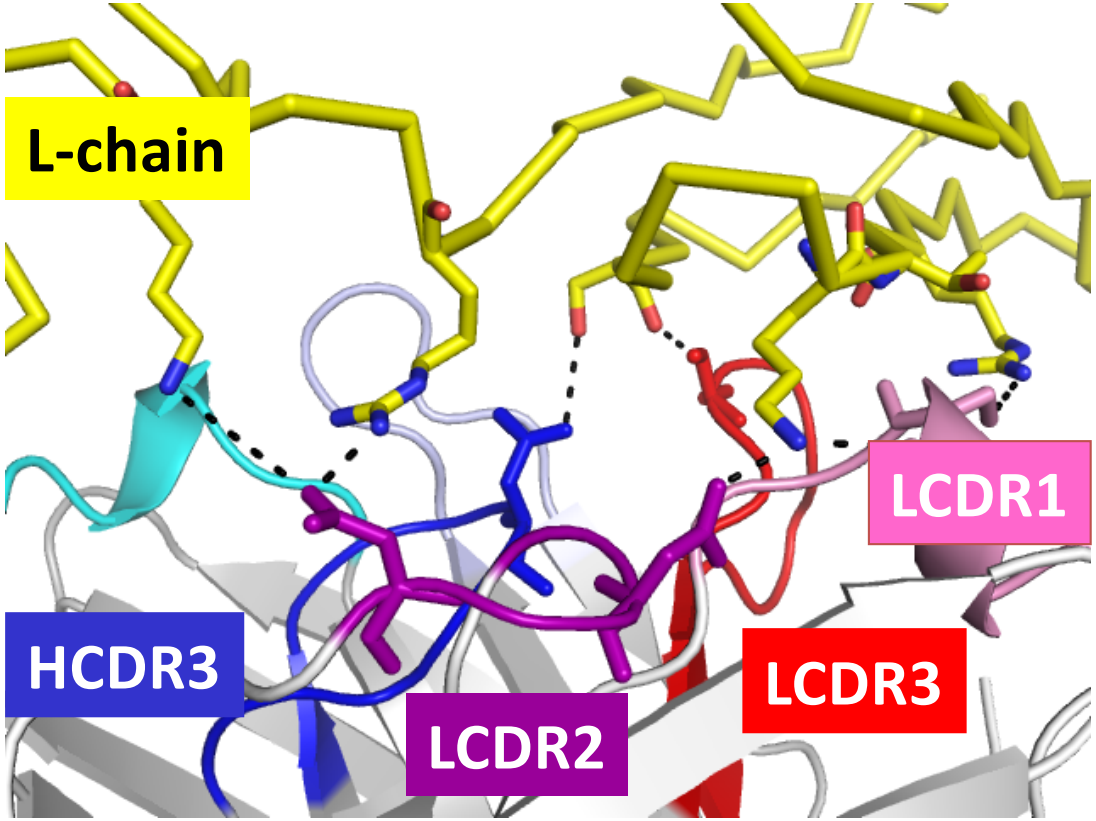
NATURE COMMUNICATIONS | 8:15746

subset #2 mAbs homodimerize



interactions are CDR-mediated

mainly by the CDR2 of **IGLV3-21**



the instructive case of subsets #2 and #169

9/acidic-3 VH CDR3

	Subset #2	Subset #169	
SHM	M-CLL U-CLL	M-CLL U-CLL	borderline
Recurrent SHM	deletion in VH CDR2	?	

present in all subset #169 cases at subclonal level
NGS analysis | Gemenetzi et al. iwCLL 2019

Murray et al. Blood 2008; Hadzidimitriou et al. Blood 2009; Darzentas et al. Leukemia 2010; Agathangelidis et al. Blood 2012; Minici et al. Nat Commun 2017

the instructive case of subsets #2 and #169

9/acidic-3 VH CDR3

	Subset #2	Subset #169	
Recurrent SHM	R-to-G at the VL-CL linker	?	critical for self-association

present in all subset #169 cases at clonal level
NGS analysis | Gemenetzi et al. iwCLL 2019

Murray et al. Blood 2008; Hadzidimitriou et al. Blood 2009; Darzentas et al. Leukemia 2010; Agathangelidis et al. Blood 2012; Minici et al. Nat Commun 2017

the instructive case of subsets #2 and #169

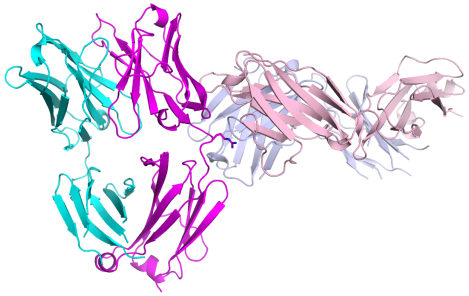
9/acidic-3 VH CDR3

Subset #2	Subset #169
45% *SF3B1* mutations	43% *SF3B1* mutations

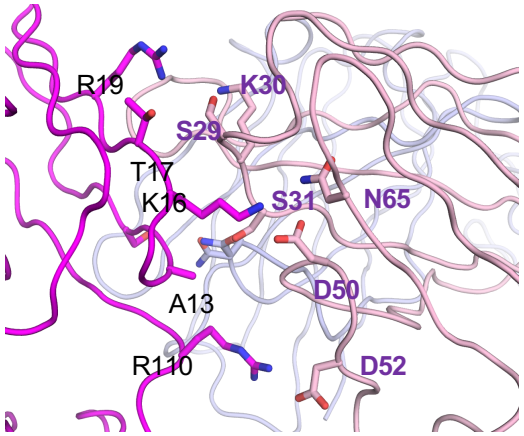
distinctive genomic background for a distinctive immunogenetic profile

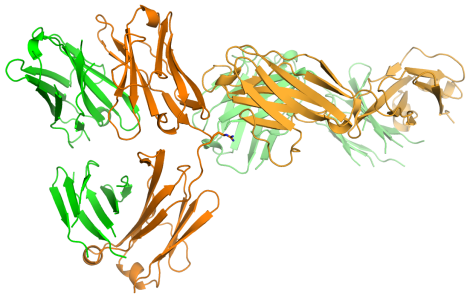
Strefford et al. Leukemia 2013; Rossi et al. Blood 2013; Baliakas et al. ASH 2015; Sutton et al. Haematologica 2016

highly similar homotypic interactions in subsets #2 and #169

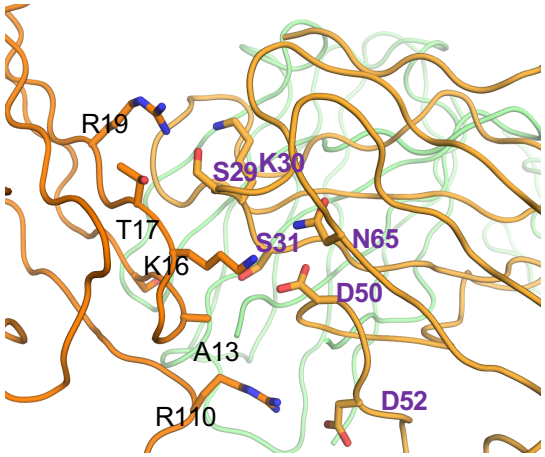


subset 2 BcR Fab





subset 169 BcR Fab



Confidential; courtesy Massimo Degano

reasonable hypothesis

satellite subsets could share similar pathophysiology

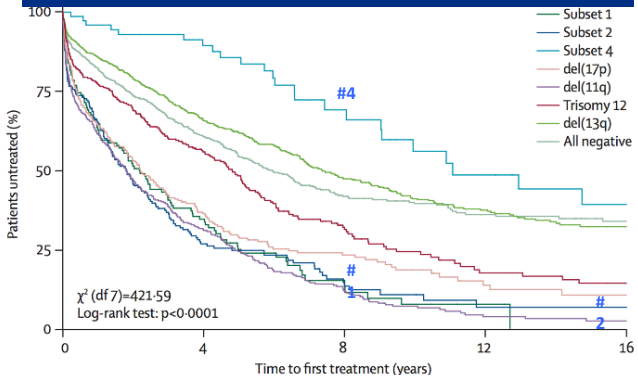
clinical question

why care for subsets?

BcR stereotypy refines risk stratification

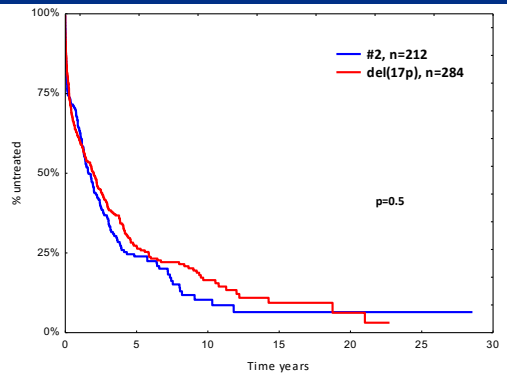
Distinct clinical outcomes for subsets #1, #2 and #4, independently of genomic aberrations or SHM status

Baliakas et al. Lancet Haematol. 2014



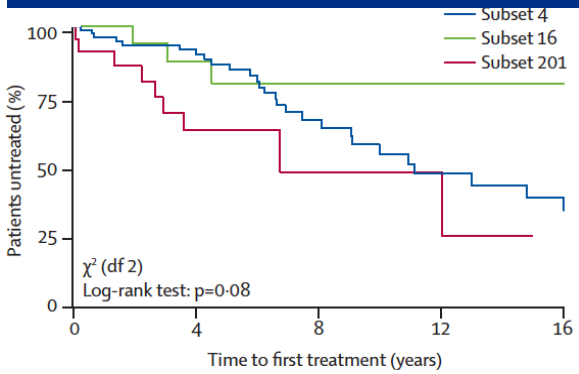
Subset #2 is as bad as CLL with TP53 aberrations though essentially devoid of such lesions

Baliakas et al. Blood 2015



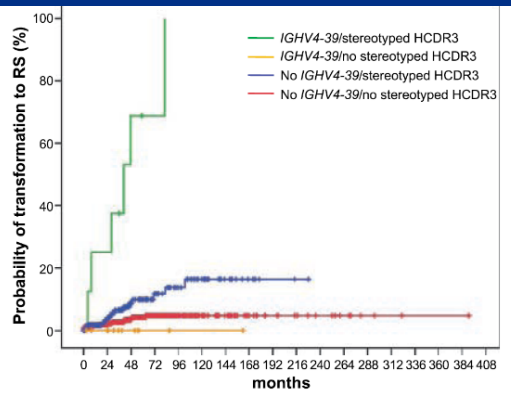
All express IGHV4-34, all concern IG mutated CLL, yet the outcome is different

Xochelli et al. Clin Cancer Res 2017



Subset #8: the highest risk for Richter's transformation amongst all CLL

Rossi et al. Clin Cancer Res. 2009



Subset #2 is an independent marker for unfavorable prognosis

assessment within prospective GCLLSG clinical trials

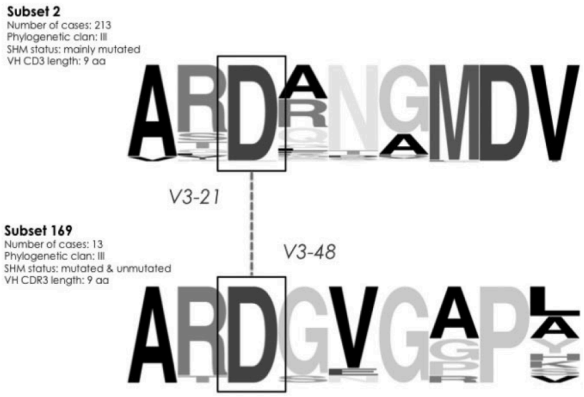
Jaramillo et al. iwCLL 2019

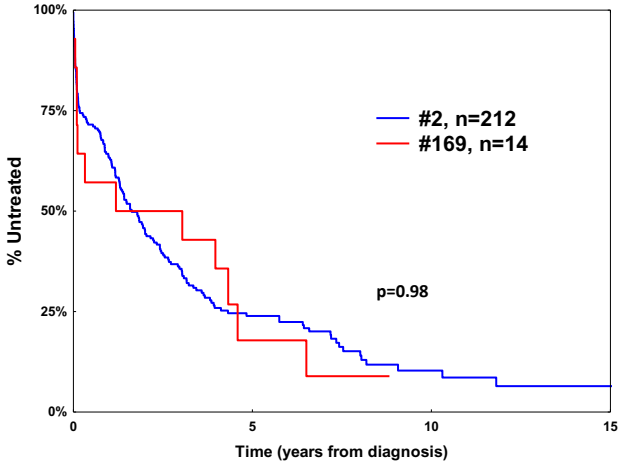
subset #2 should be proposed for risk stratification of patients

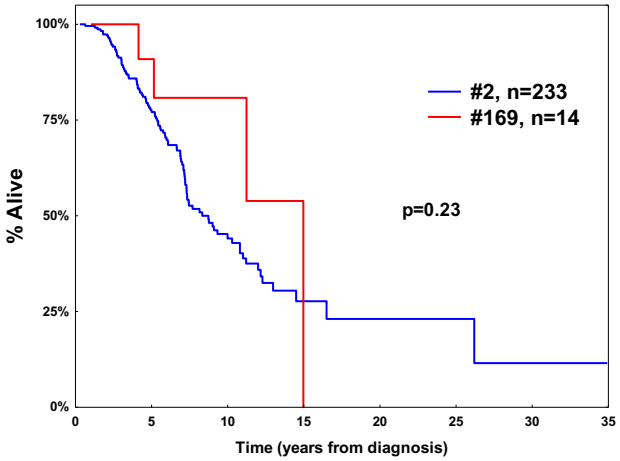
subset #2 patients do not benefit from chemo immunotherapy

the instructive case of subsets #2 and #169

9/acidic-3 VH CDR3







similar clinical courses and outcomes

Baliakas et al. unpublished data

argument

satellite subsets could share similar pathophysiology,
reflected in a **similar clonal behavior**

implications for risk stratification

conclusions and (reasonable) speculations

BCR IG stereotypy…

is the strongest molecular evidence for antigen selection in CLL ontogeny

is a powerful means for breaking down CLL into subsets with homogeneous profiles

has contributed to the identification of distinct pathobiological mechanisms and processes shaping the clonal history in each subset

may prove key to overcoming the remarkable heterogeneity of CLL

emerges as relevant for implementing tailored therapeutic approaches in line with the principle of precision medicine

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