Biology of High-Risk Chronic Lymphocytic Leukemia

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Unmet challenges in high risk hematological malignancies: from benchside to clinical practice (2nd edition)

Turin, September 13-14, 2021

AO S.Croce e Carle
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NATIONAL CANCER INSTITUTE

high-risk cancer

(hy-risk KAN-ser)

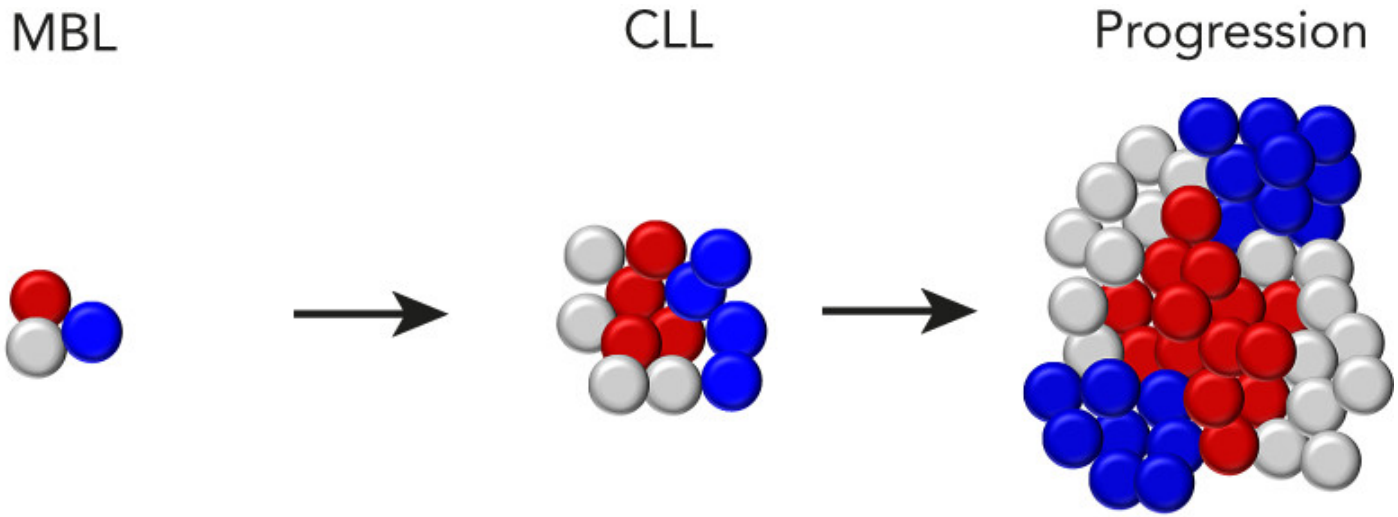
Cancer that is likely to recur (come back), or spread.

Why does cancer recur or spread?

- standard treatments are inadequate in the short or long run;

Why current treatments are inadequate?

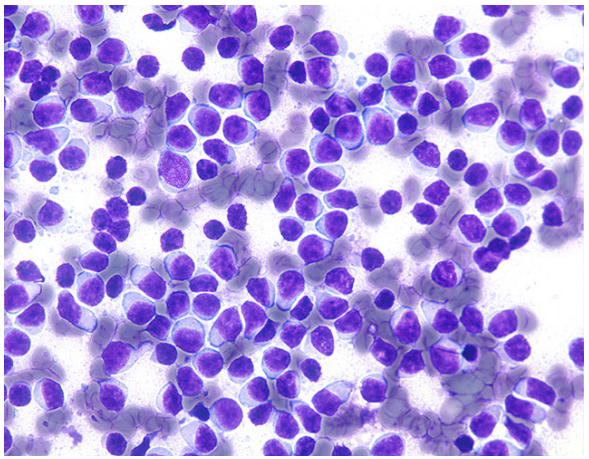
- unable to fully abrogate mechanisms of disease progression;
- CLL is heterogenous clonal disease under continuous evolution;

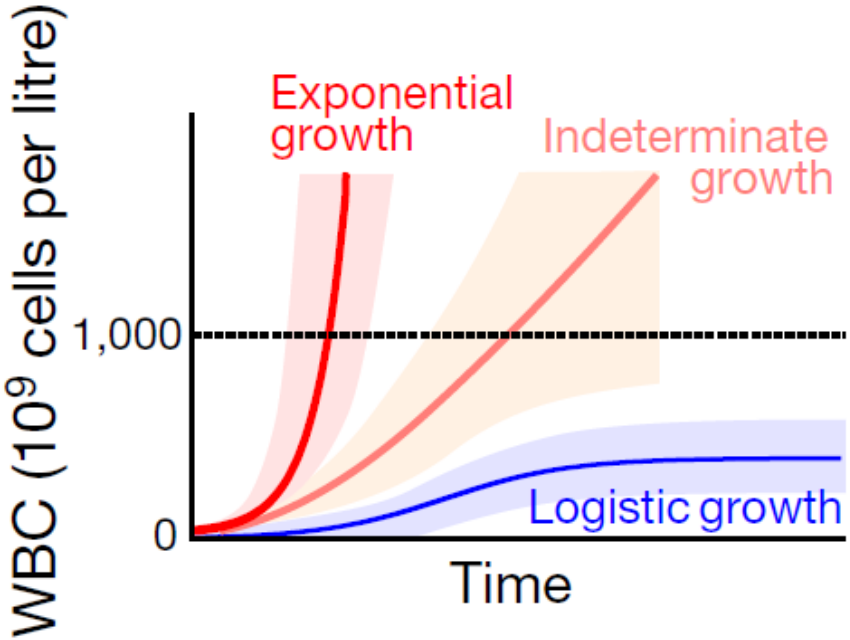


Condoluci A,et al., *J Natl Compr Canc Netw*. 2020 Dec 31;19(2):227-233.

CLL paradigm shift

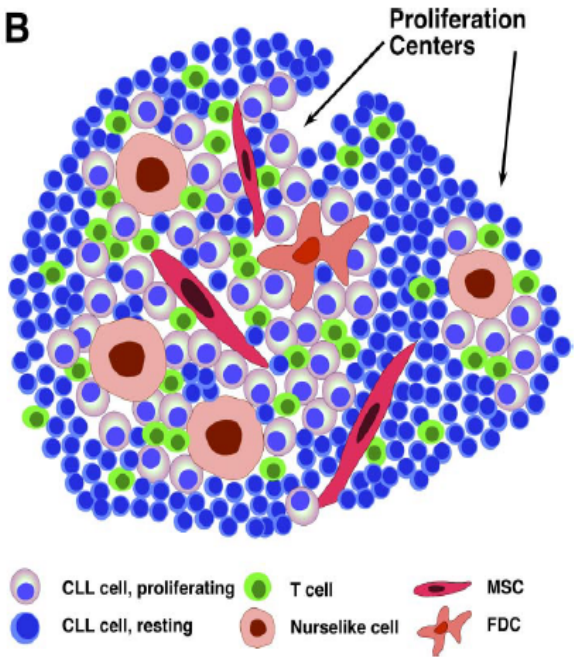
progressive accumulation of functionally incompetent lymphocytes





Gruber M et al., *Nature.* 2019 Jun;570(7762):474-479

CLL proliferation centers



Burger et al., *Blood.* 2009;114:3367-3375

Drivers of disease progression in CLL:

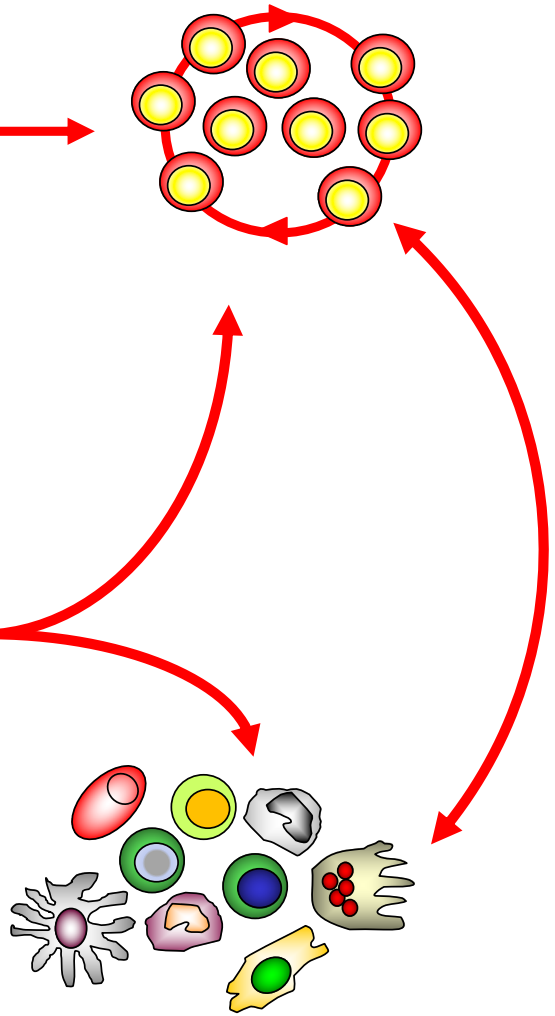
Intrinsic drivers:

- genetic instability
- BCR (IGHV-M/UM)
- genetic abnormalities
- epigenetic alterations

Extrinsic drivers:

- treatments

- microenvironment interactions



Massaia M, 2021

Drivers of disease progression in CLL:

Innate high-risk (primary)

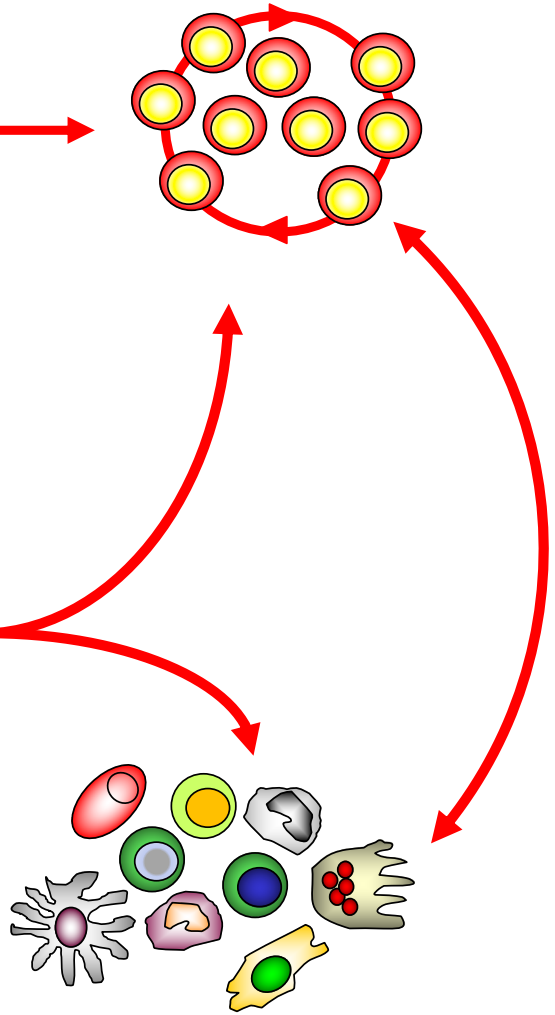
Intrinsic drivers:

- genetic instability
- BCR (IGHV-M/UM)
- genetic abnormalities
- epigenetic alterations

Extrinsic drivers:

- treatments 

- microenvironment interactions



Massaia M, 2021

Drivers of disease progression in CLL:

Innate high-risk (primary)

Adaptive high-risk (secondary)

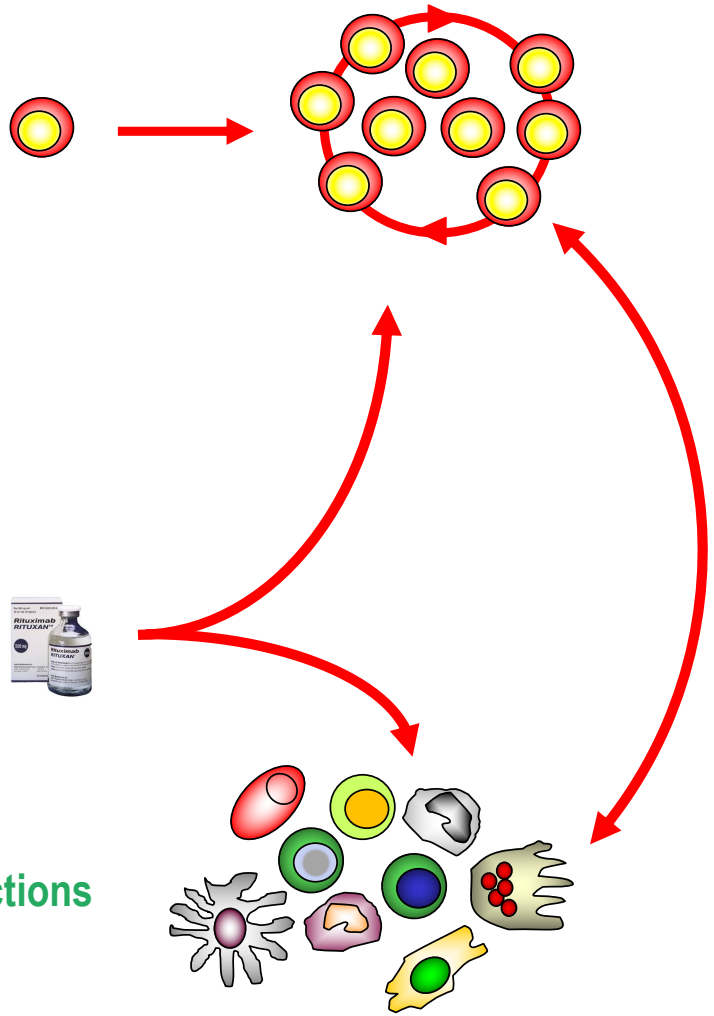
Intrinsic drivers:

- genetic instability
- BCR (IGHV-M/UM)
- genetic abnormalities
- epigenetic alterations

Extrinsic drivers:

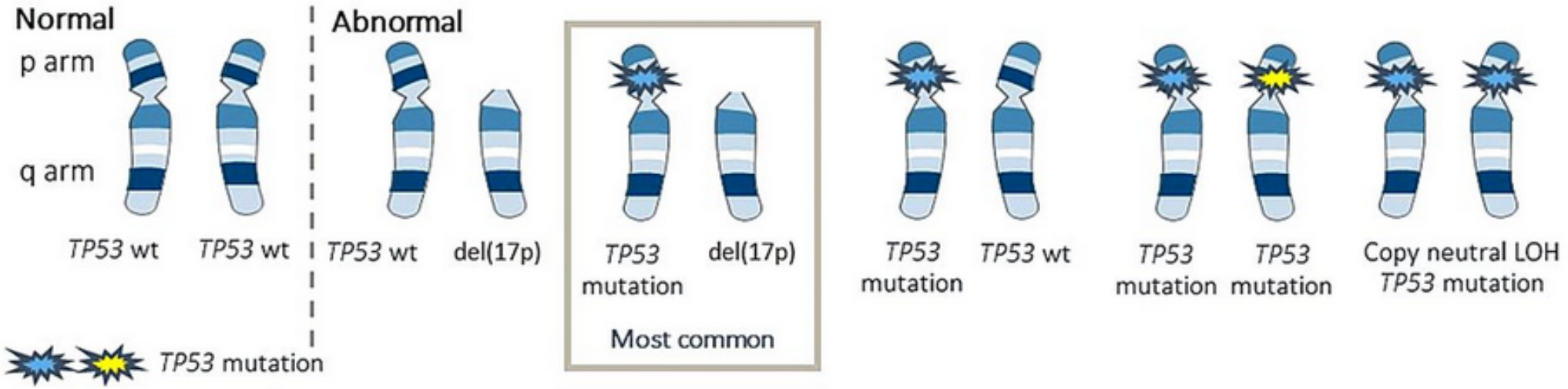
- treatments

- microenvironment interactions



Massaia M, 2021

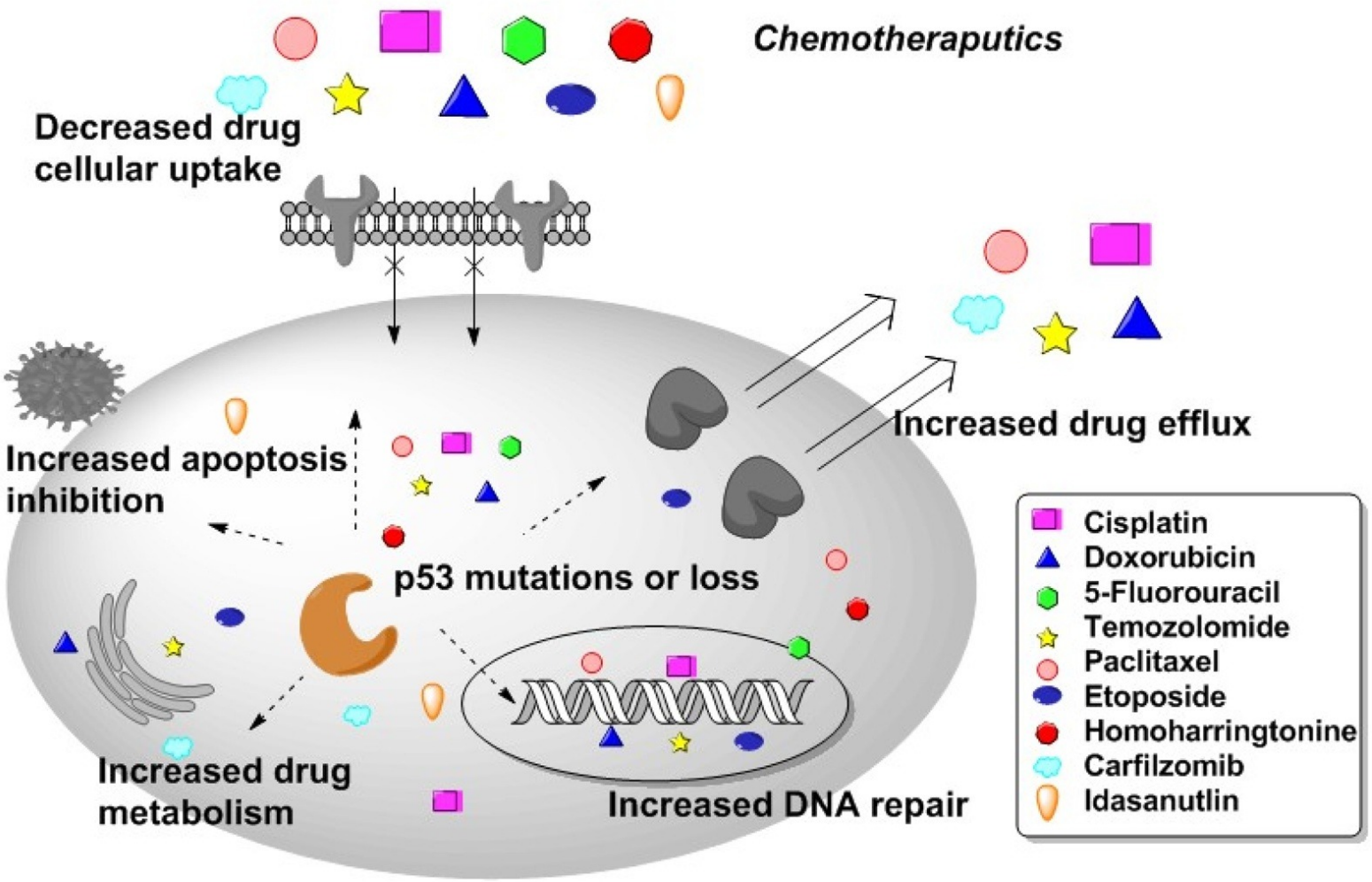
TP53 aberrations in CLL



Proportion of all TP53 aberations (%)	~10%	~60%	~30%

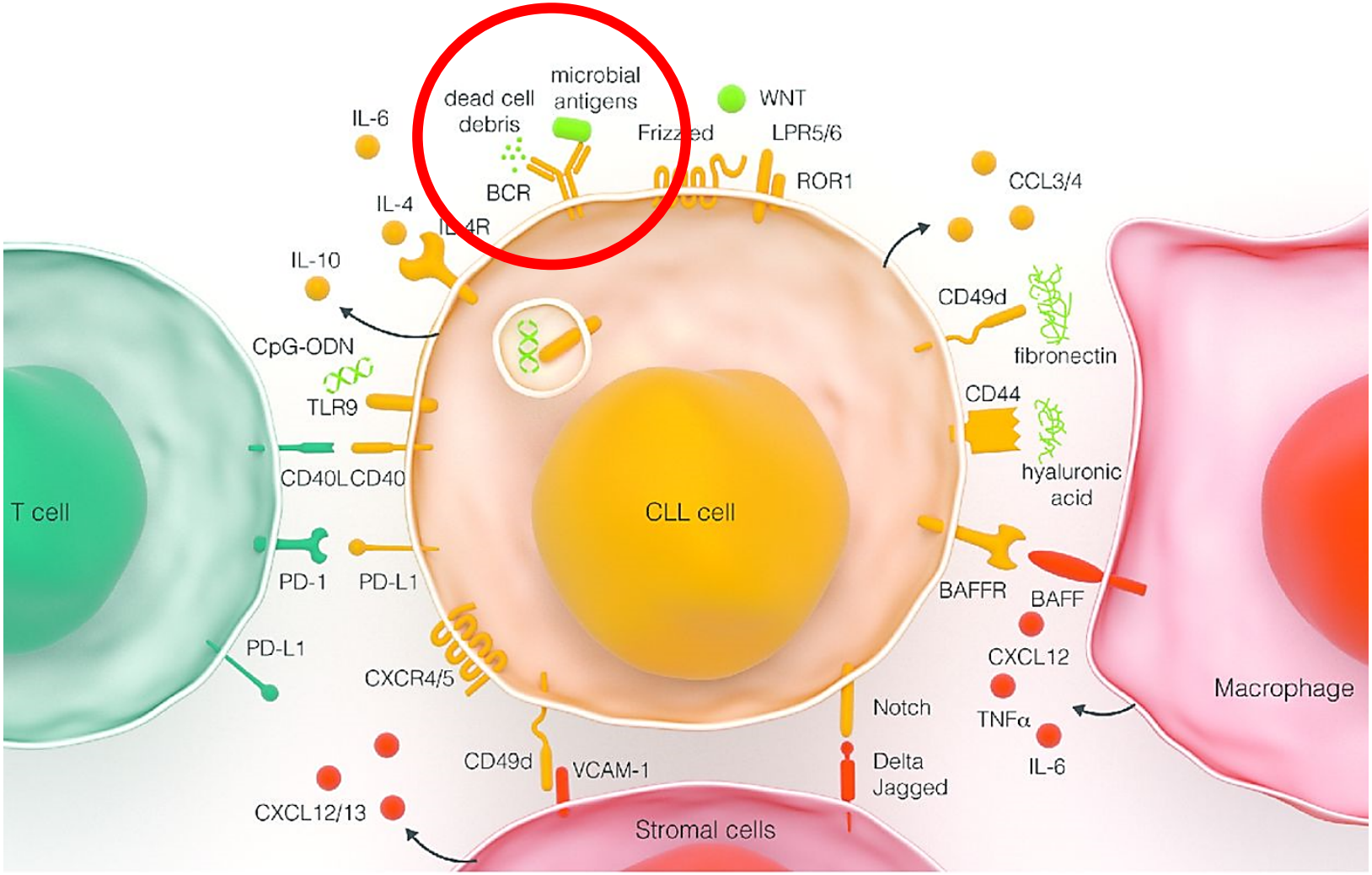
Campo E et al. *Haematologica.* 2018 Dec;103(12):1956-1968

Mechanisms for p53 mutation-associated chemotherapy resistance



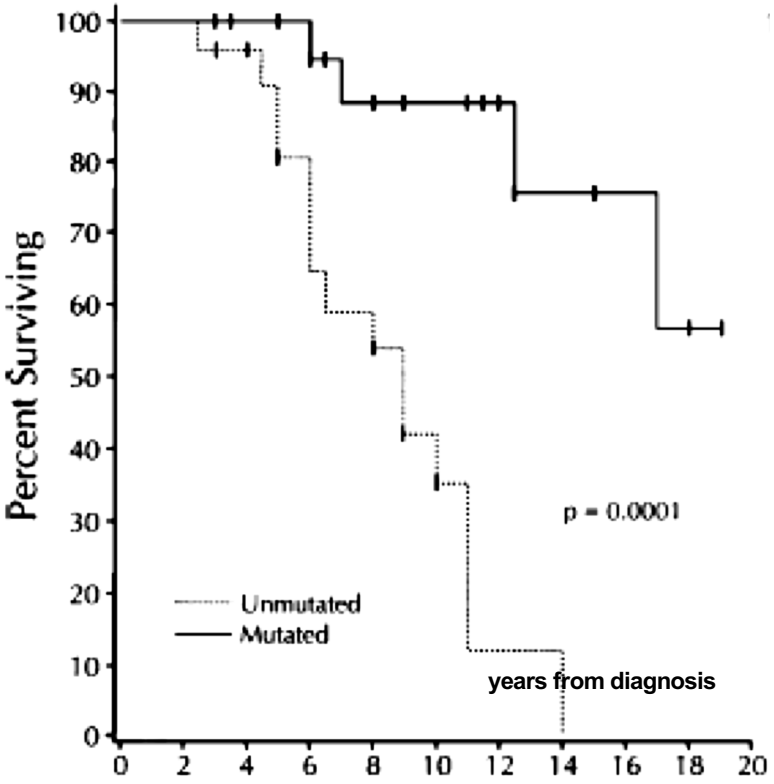
Cao X et al., *Drug Resist Updat*. 2020 Mar;49:100671.

CLL cell interactions in the TME

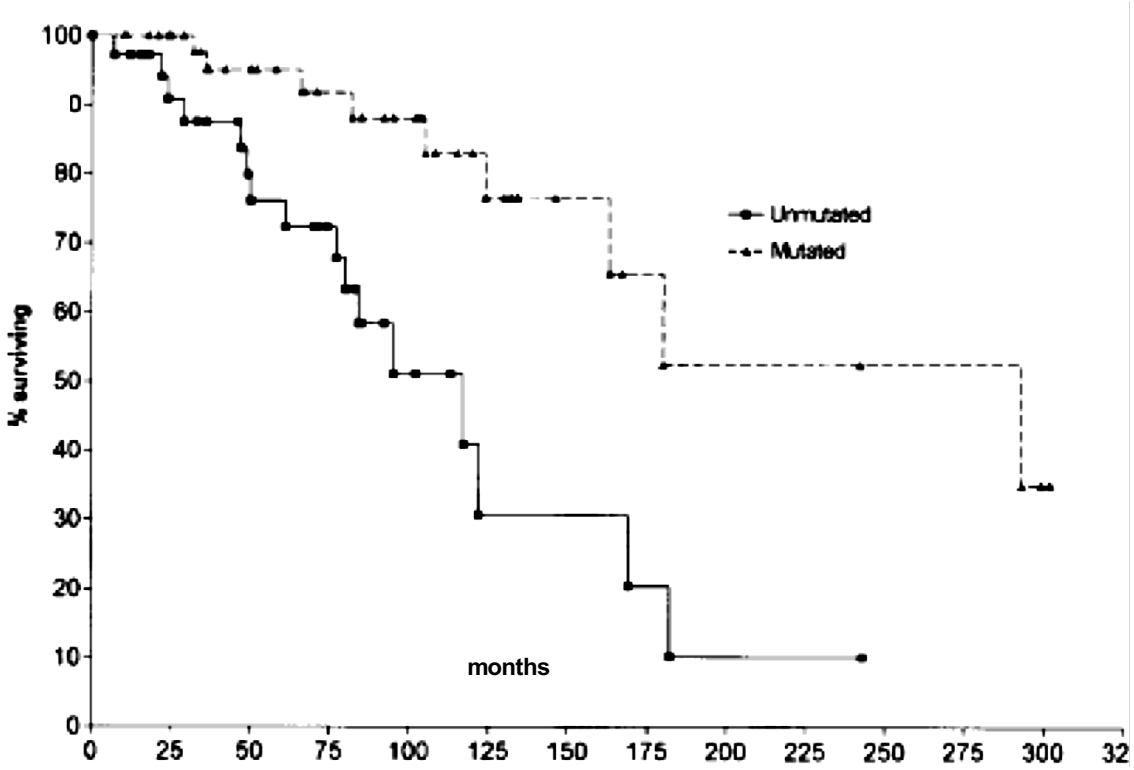


Wiestner A. *Haematologica.* 2015 Dec;100(12):1495-507

Prognostic significance of IgVH mutational status in CLL

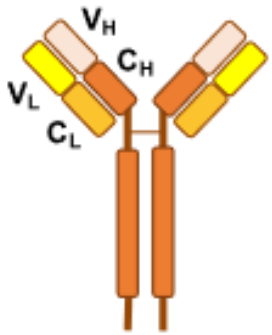
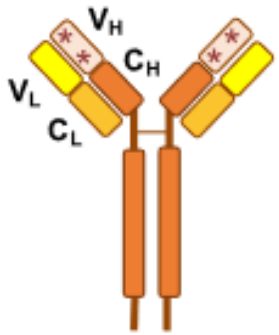


Damle RN et al., *Blood* 94: 1840-1847, 1999



Hamblin TJ et al., *Blood* 94: 1848-1854, 1999

Characteristics of U-CLL and M-CLL patient subsets

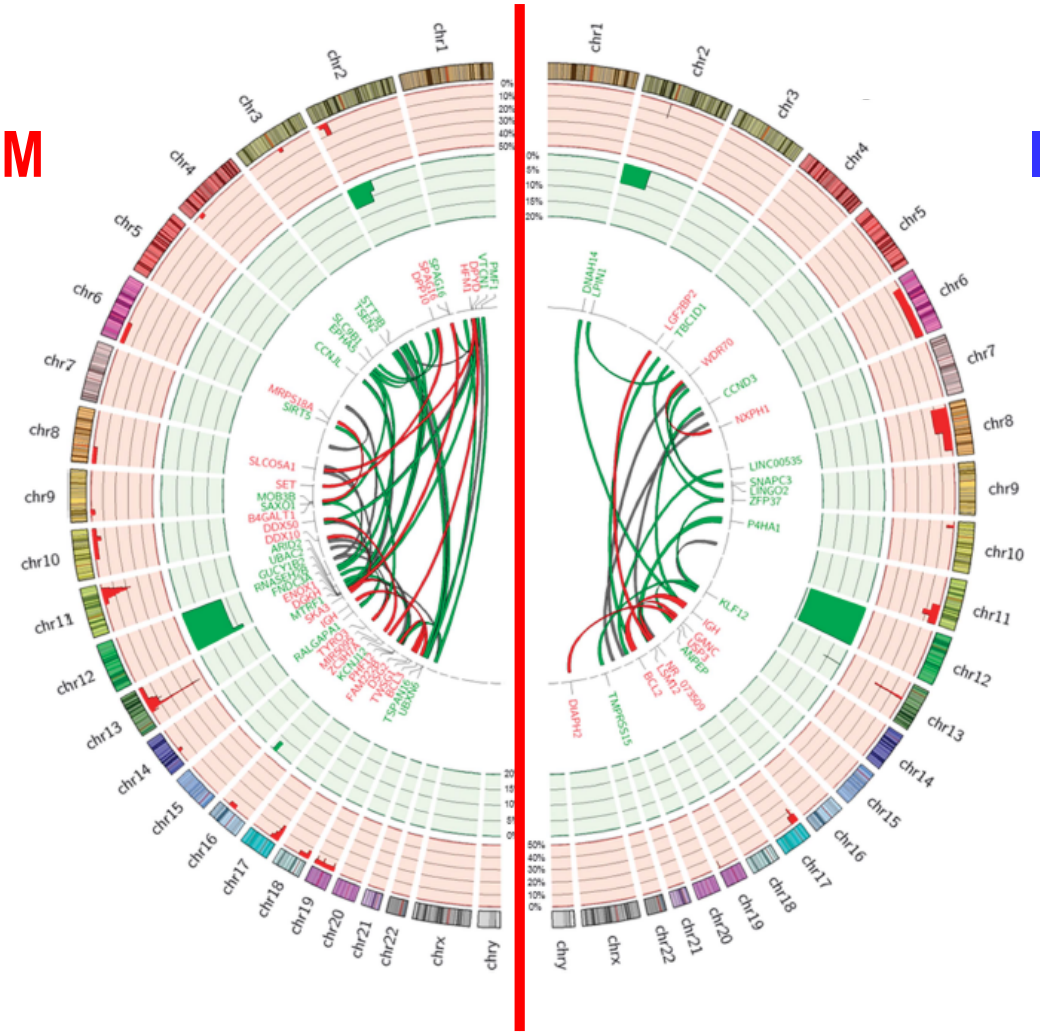
U-CLL		M-CLL
		
40%	CLL patient frequency	60%
≥98%	Homology with germline IGHV	<98%
High	BCR responsiveness	Low, anergic BCRs
Autoantigens, high poly-reactivity	Antigenic determinants	Microbial/Autoantigens, higher BCR specificity

Ten Hacken E et al., *Leukemia*. 2019 Feb;33(2):287-298.

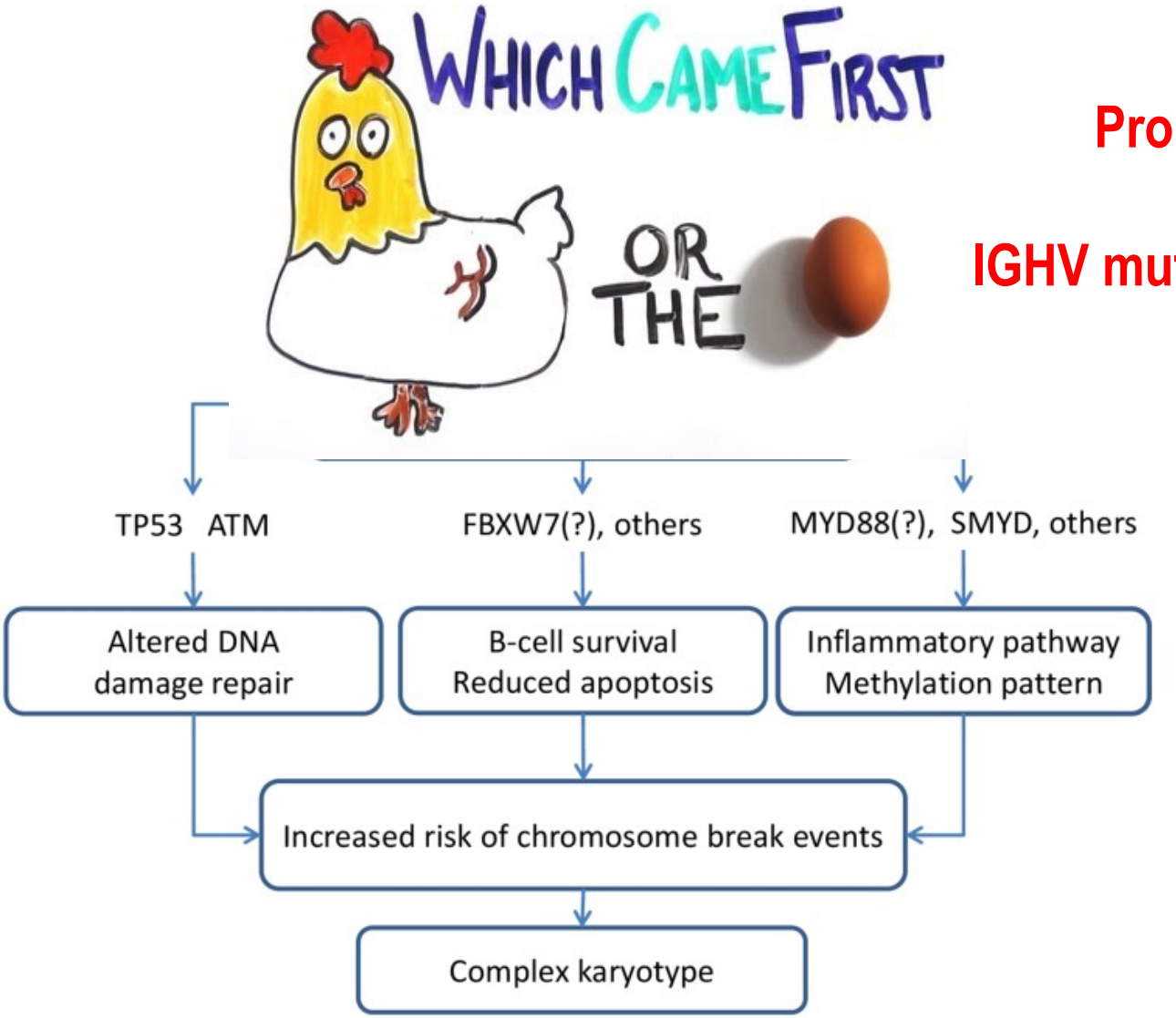
Distinct mutational landscapes by WGS in IGHV-M and IGHV-UM CLL

IGHV-UM

IGHV-M



Burns et al., *Leukemia* (2018) 32, 332–342



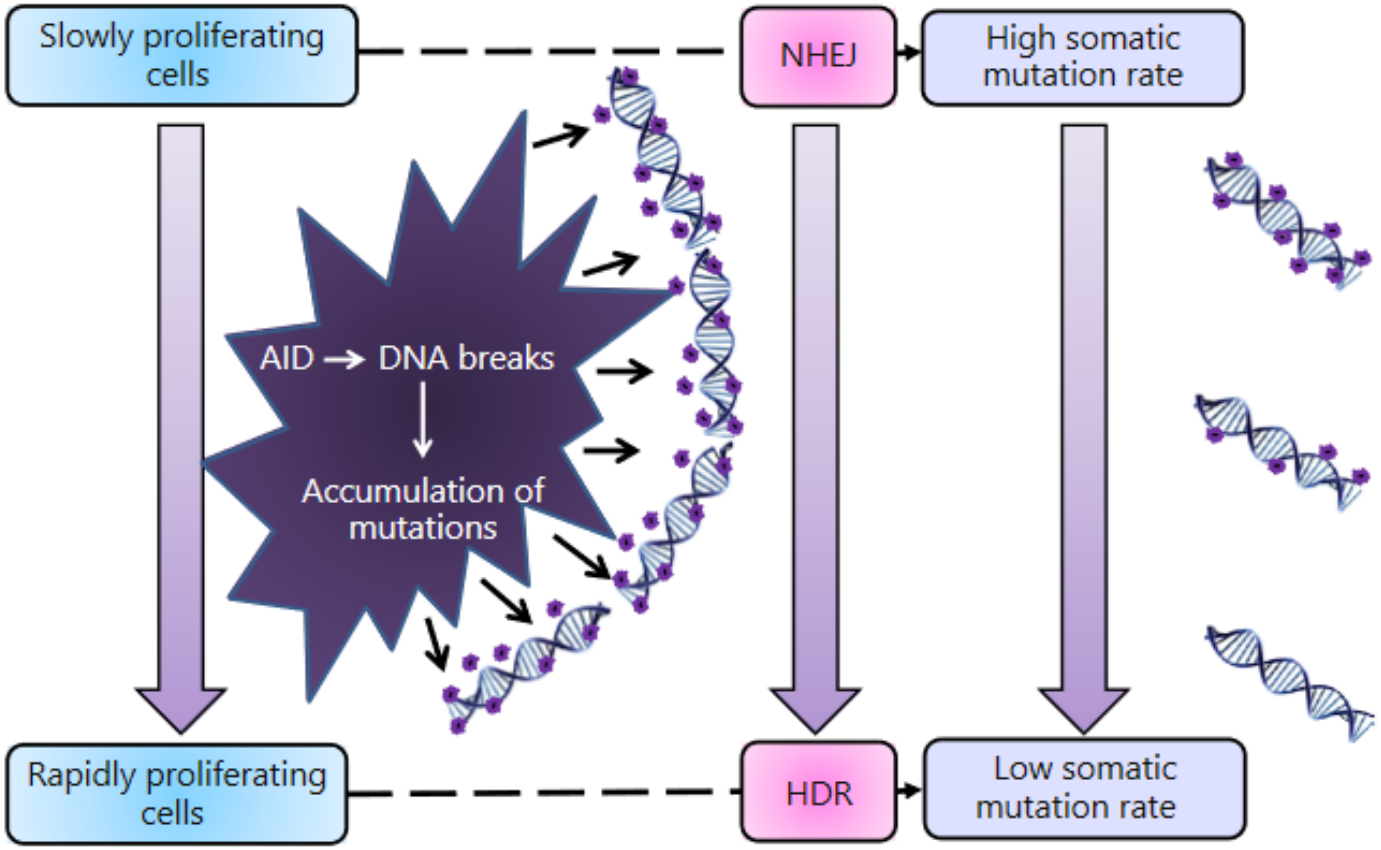
Proliferation
or
IGHV mutational status

?

Cavallari M et al., *Oncotarget*. 2018 Sep 28;9(76):34398-34412.

The IGHV mutations status is determined by the proliferation rate

nonhomology end-joining (NHEJ) repair → low fidelity mechanism

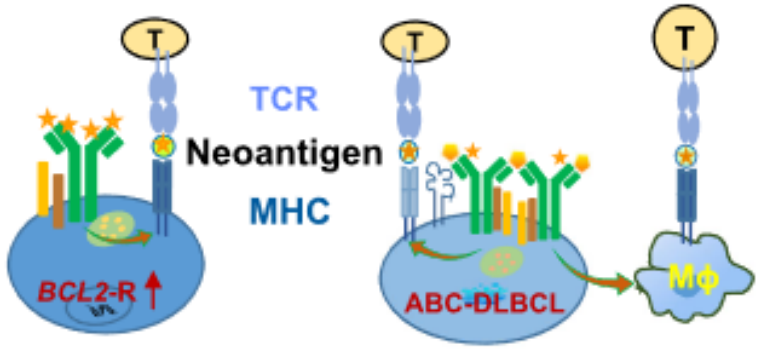


homology-directed repair (HDR) → high fidelity mechanism

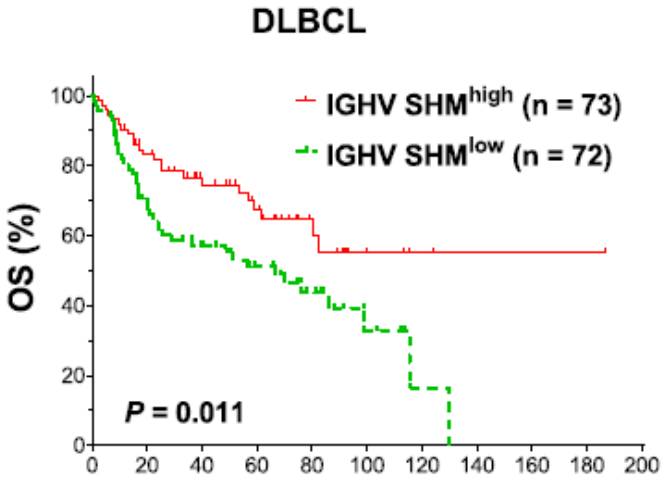
Rozovski U, et al. *Acta Haematol*. 2018;140(1):51-54.

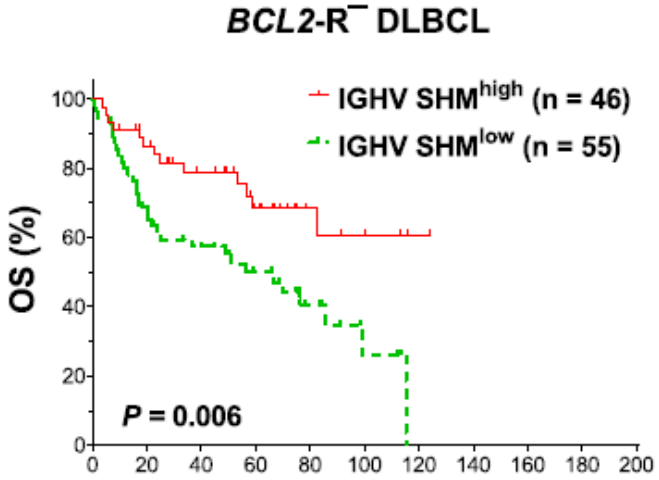
Immunogenicity potential of IGHV-derived neoantigens generated by SHM

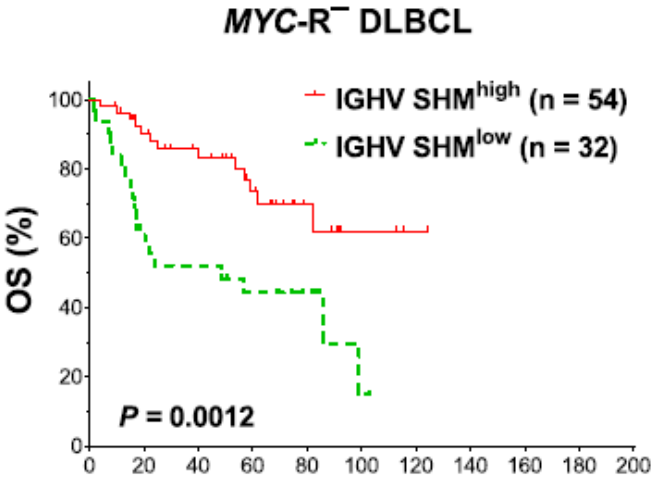
IGHV SHM^{high}: >8% nt
Prevalence: ~50%



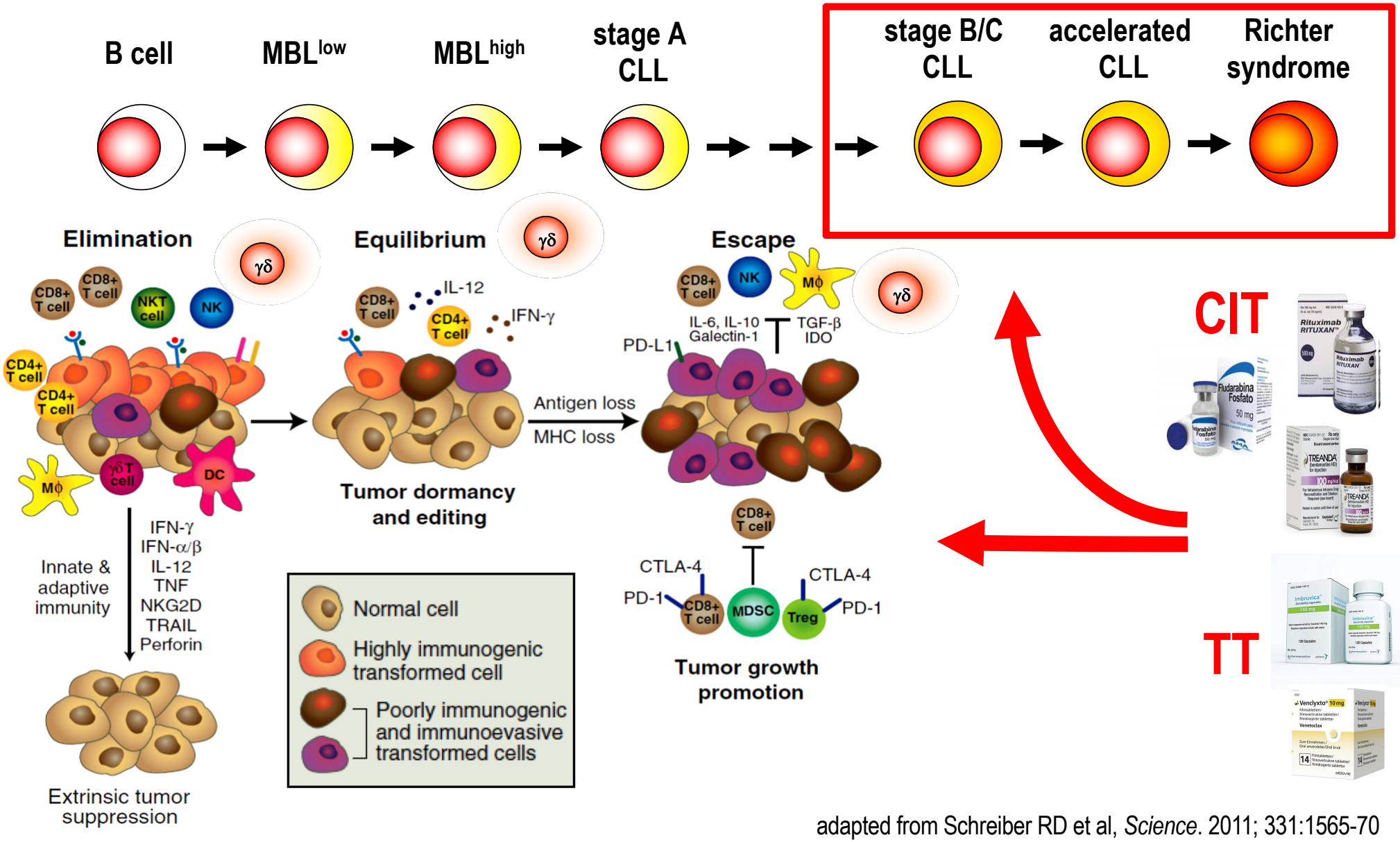
Neoantigens ↑ Rare T cell-exposed motifs ↑
PD-1^{+} % in T cells in ABC-DLBCL ↓
Longer survival of patients in overall DLBCL, ABC-DLBCL, and cases lacking *BCL2* or *MYC* rearrangement





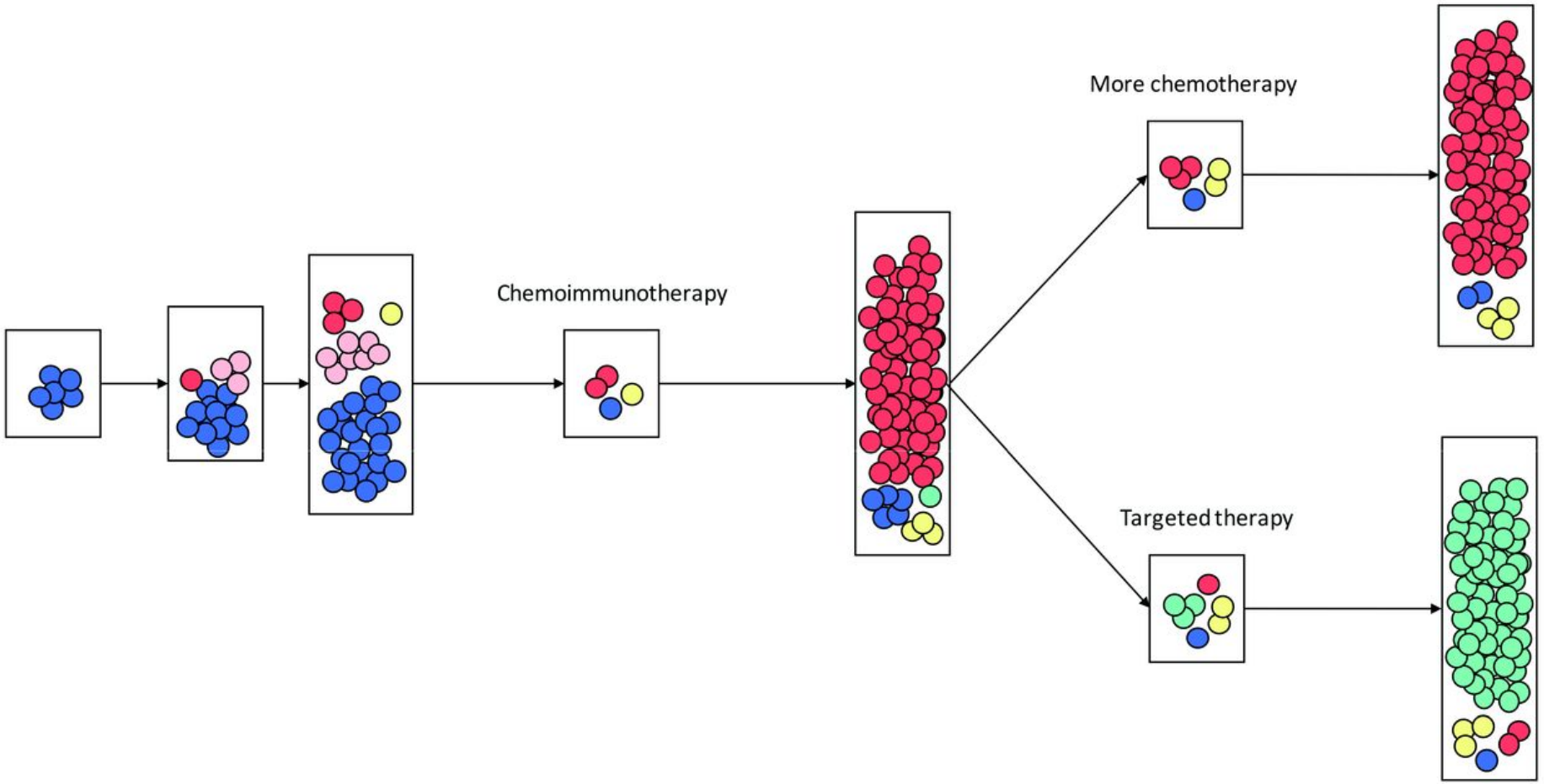


Xu-Monette ZY et al., *J Immunother Cancer*. 2019 Oct 22;7(1):272.



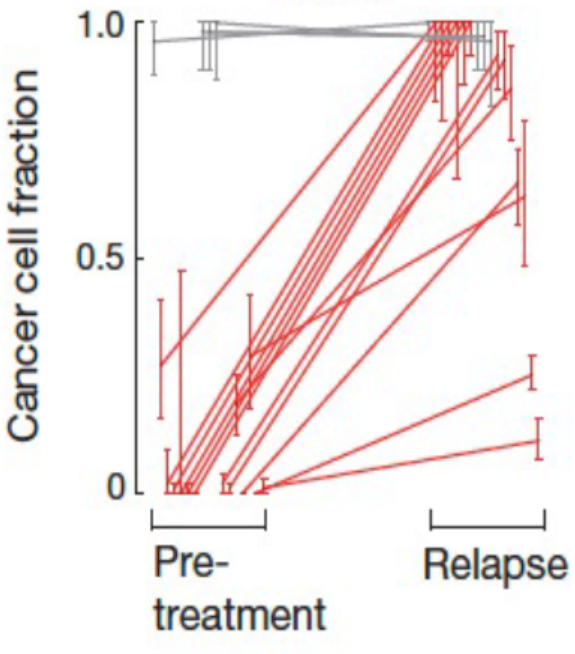
adapted from Schreiber RD et al, *Science*. 2011; 331:1565-70

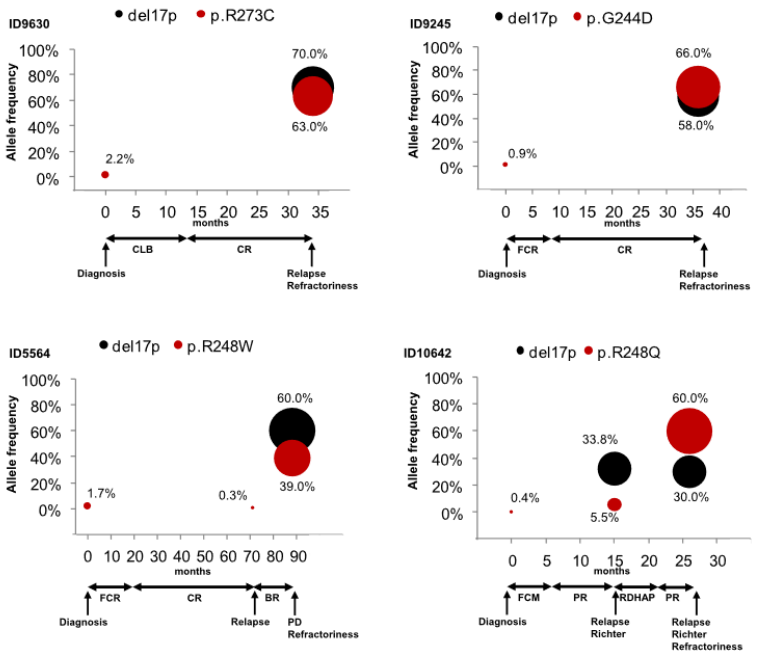
Clonal selection is driven by different treatment regimens.

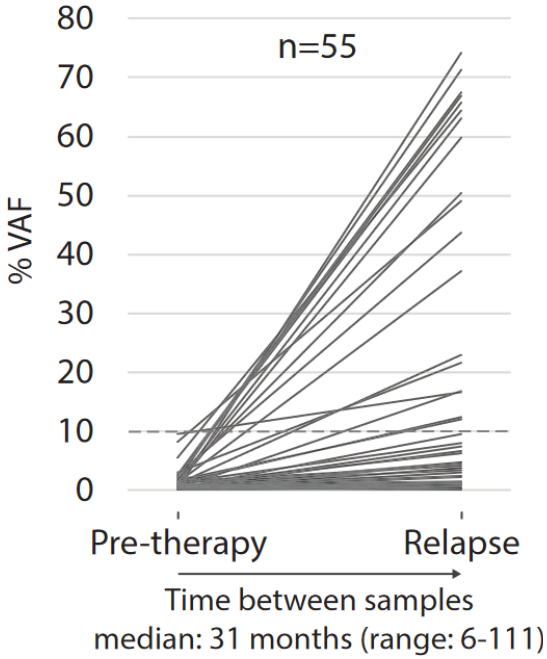


Modified from Campo E et al. *Haematologica.* 2018 Dec;103(12):1956-1968

CIT-induced clonal expansion of *TP53 mutants*







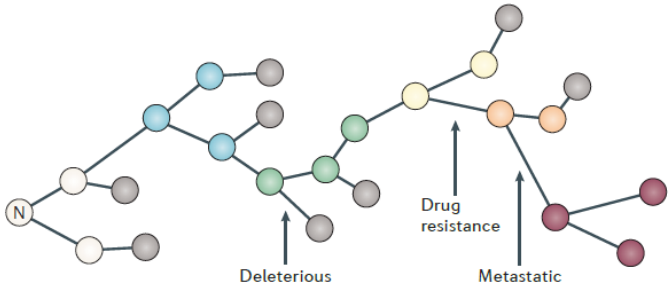
Landau DA et al., *Nature*. 2015 Oct 22;526(7574):525-30.

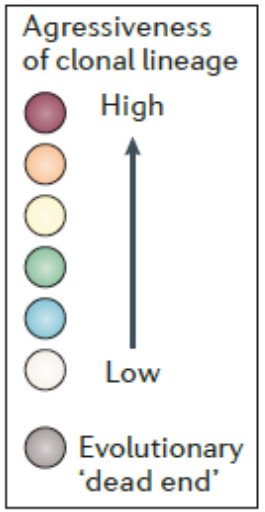
Rossi D et al., *Blood*. 2014 Apr 3;123(14):2139-47

Malcikova J et al., *Blood*. 2021 May 4; pub ahead of print

Alternative clonal evolution models to survive in the TME

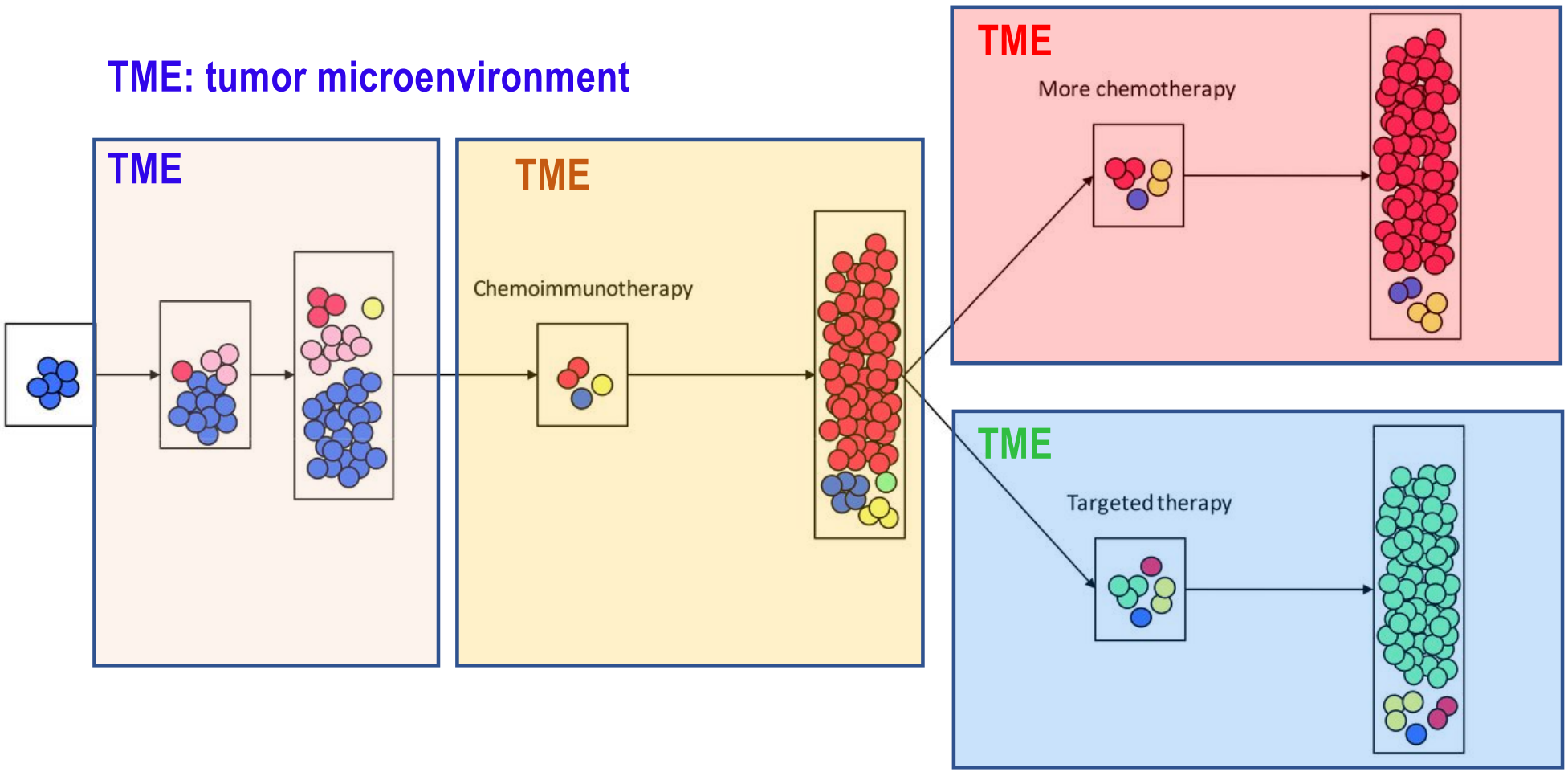
Clonal evolution model





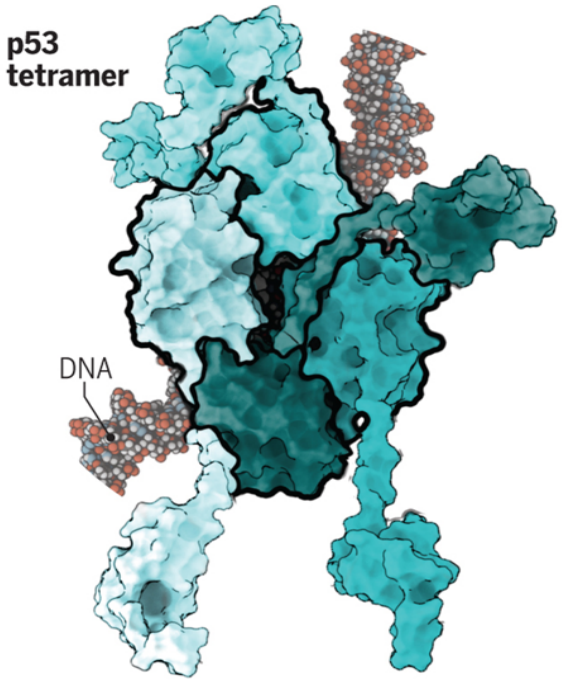
Korolev KS et al., *Nat Rev Cancer*. 2014 May;14(5):371-80.

TME: tumor microenvironment



Modified from Campo E et al. *Haematologica.* 2018 Dec;103(12):1956-1968

Effects of TP53 mutations



Wild-type p53
Wild-type (WT) p53 is a tetrameric transcription factor.

DNE mutant/ wild type
Mutation in one allele can cause DNEs in which the mutant (MT) dimer poisons the wild-type dimer.

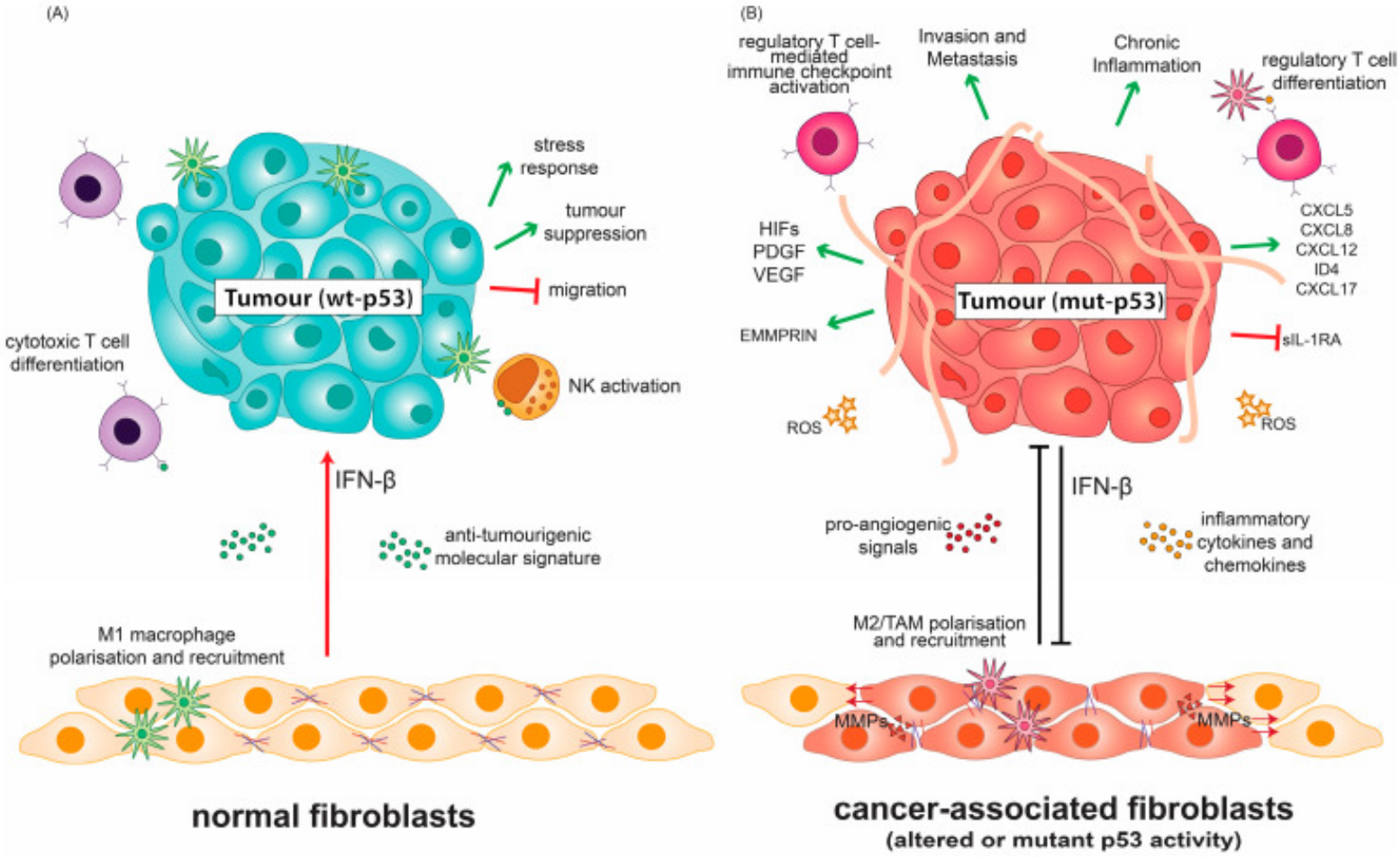
p53 LOF mutant
An all-mutant tetramer may have LOF of wild-type activity.

p53 GOF mutant
All-mutant tetramers may show GOF through new protein interactions with protein X.

DNE: dominant negative effects;
LOF: loss of function;
GOF: gain of function;

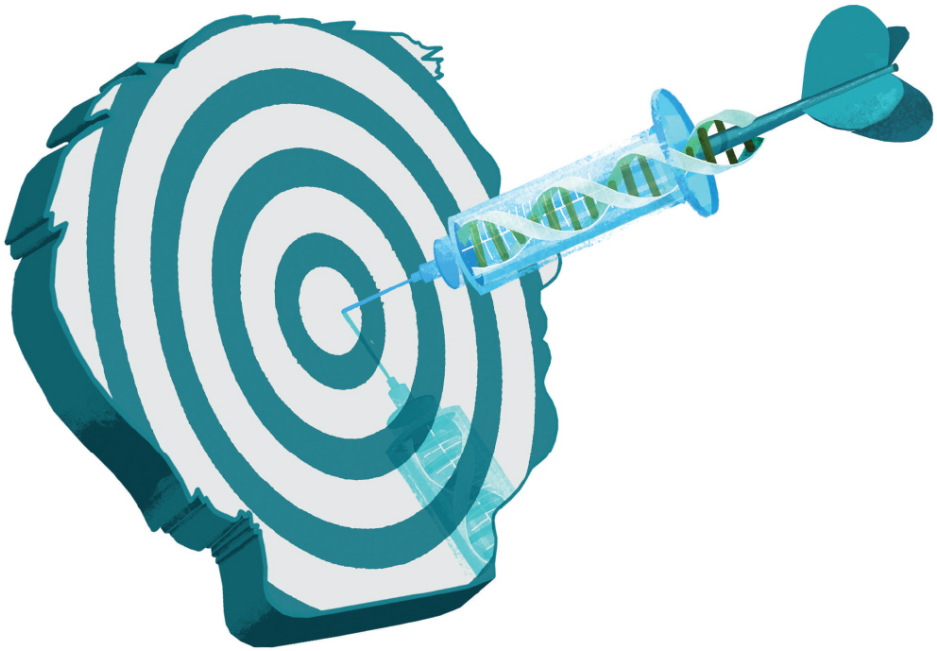
Lane DP. Et al., *Science*. 2019 Aug 9;365(6453):539-540.

Mutant p53 modifies the TME to suppress immune responses

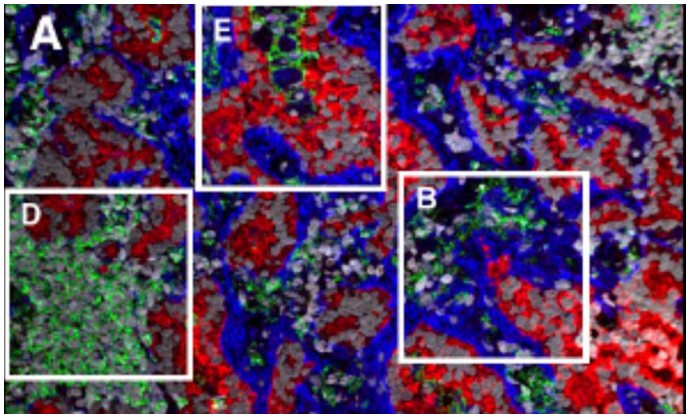


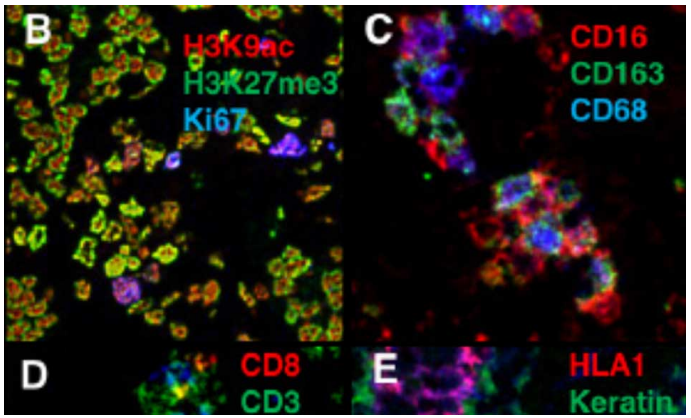
Agupitan AD et al., *Int J Mol Sci*. 2020 May 13;21(10):3452.

Precision Medicine

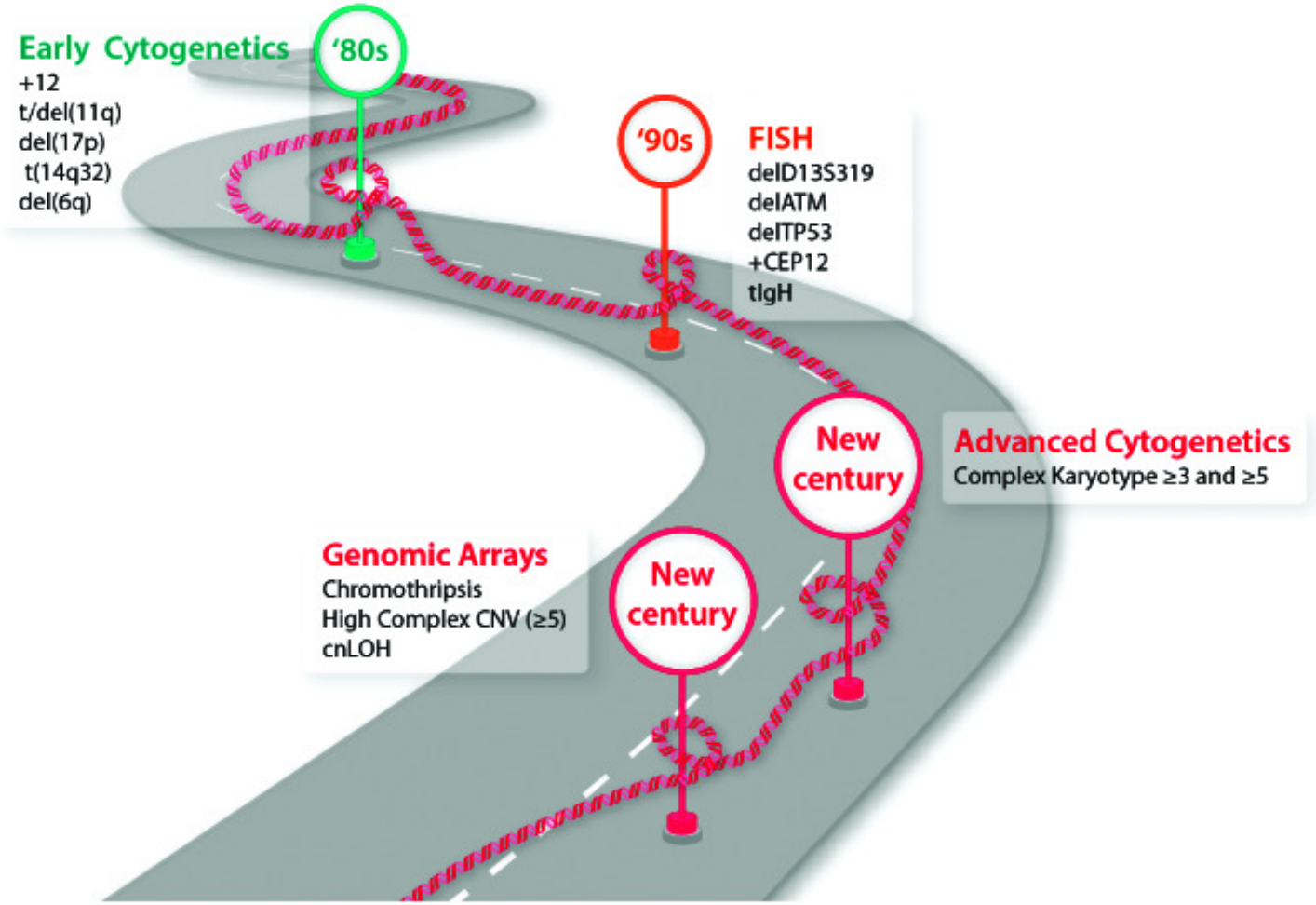


Precision Immunology





The long road of genetic advances with a clinical impact on CLL



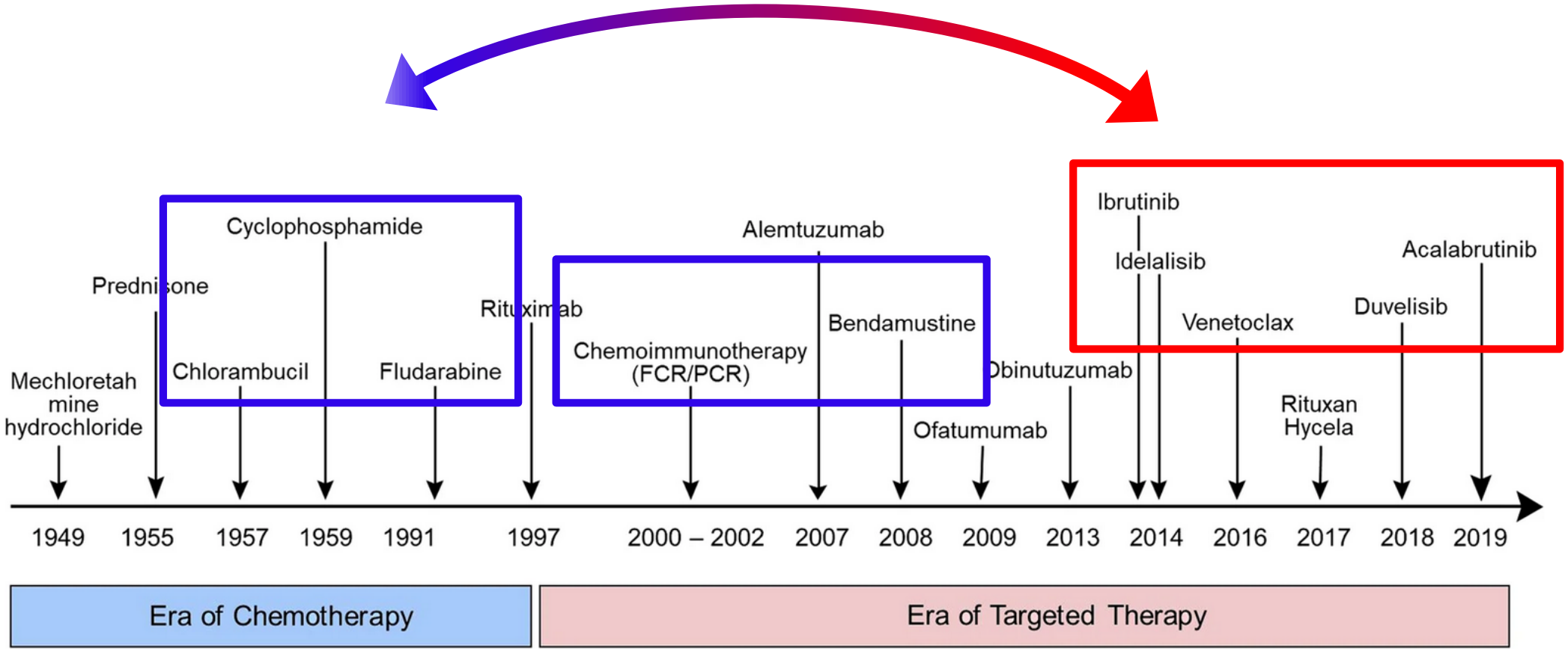
Cuneo A et al., *Haematologica*. 2021 Jan 1;106(1):7-9.

The evolutionary concept of high-risk CLL

Discovery of intrinsic high-risk factors ⟷ Discovery of extrinsic high-risk Factors (TME) ⟷ Drug development

Massaia M, 2021

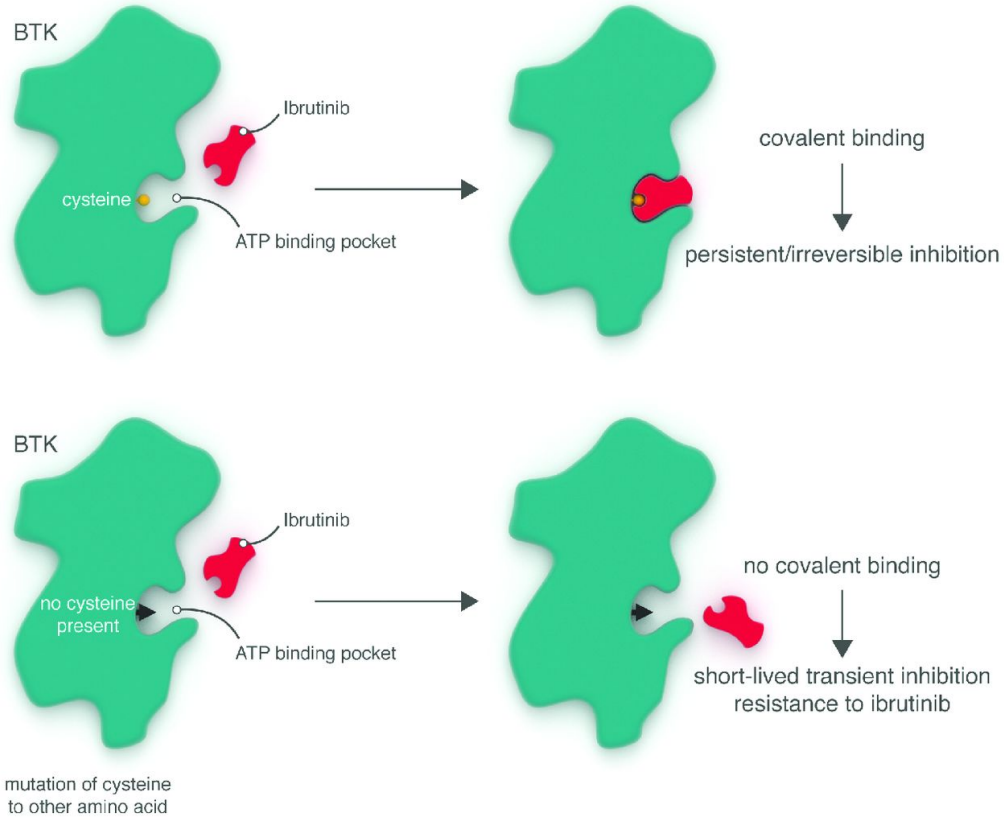
Paradigm shift of high-risk concept in CLL



adapted from Parikh, S.A. et al., *Leukemia* **34,** 1979–1983 (2020)

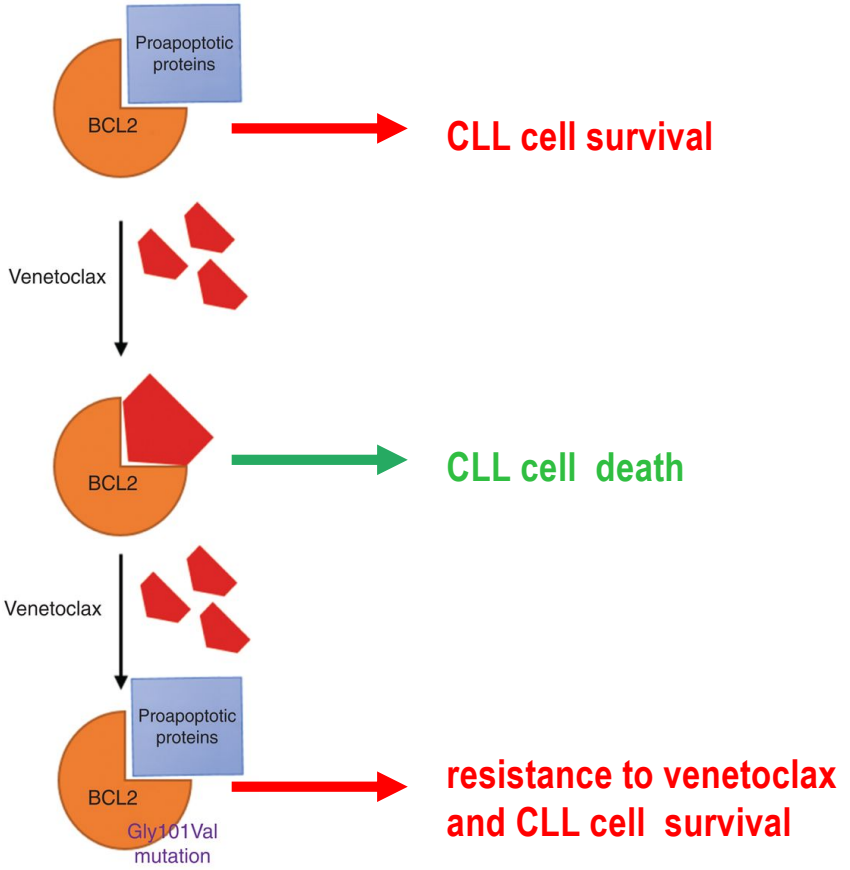
Targeted therapy is not exempted from acquired resistance

ibrutinib



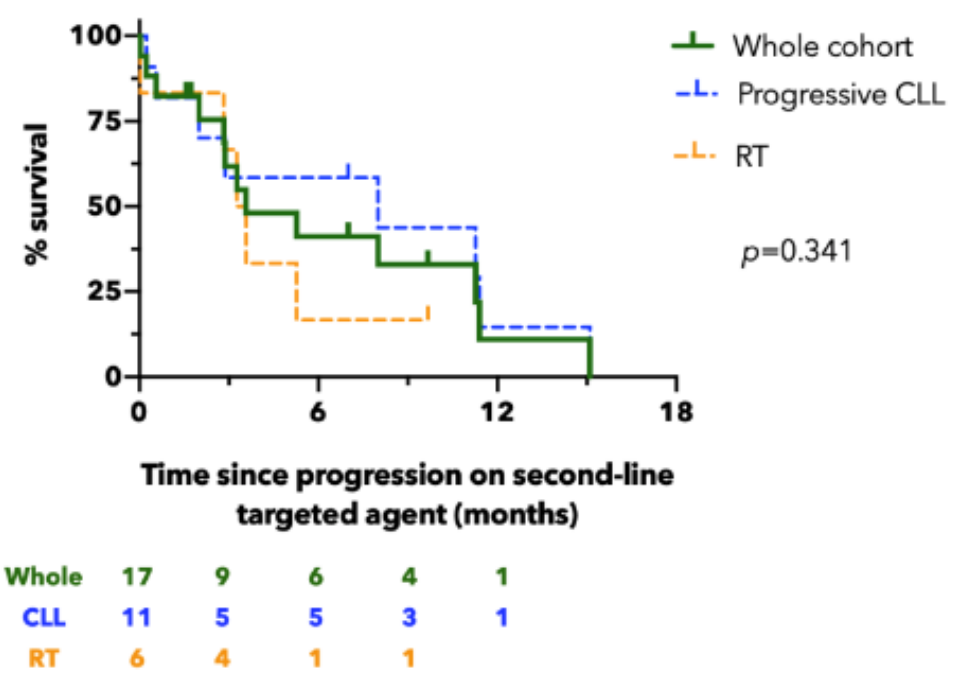
Zhang SQ et al., ,*Br J Haematol*. 2015 Aug;170(4):445-56.

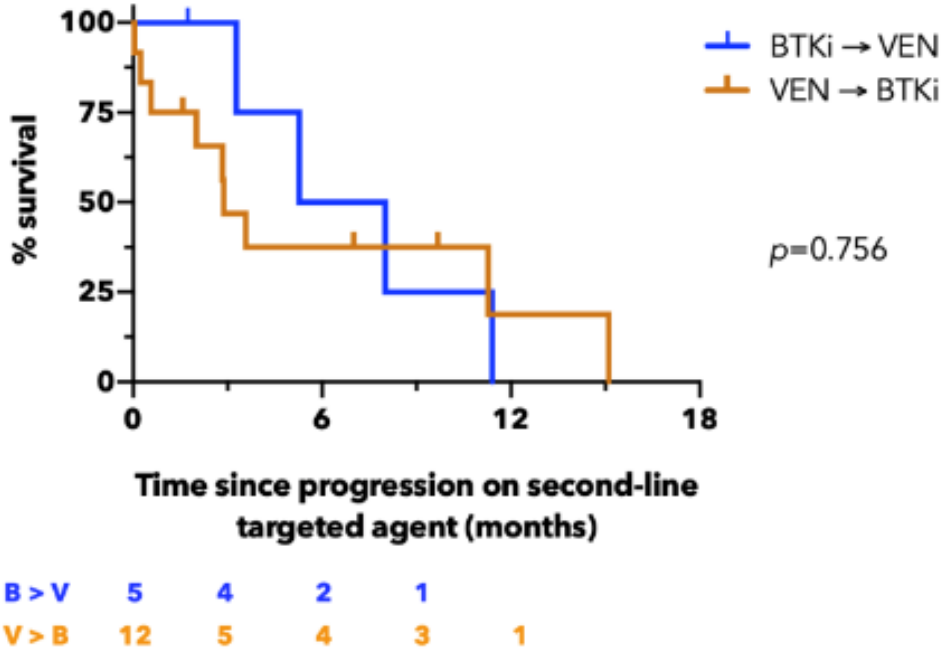
venetoclax



modified from Thangavadivel S et al., *Cancer Discov*. 2019 Mar;9(3):320-322.

Dismal prognosis of CLL pts resistant to BTKi and venetoclax

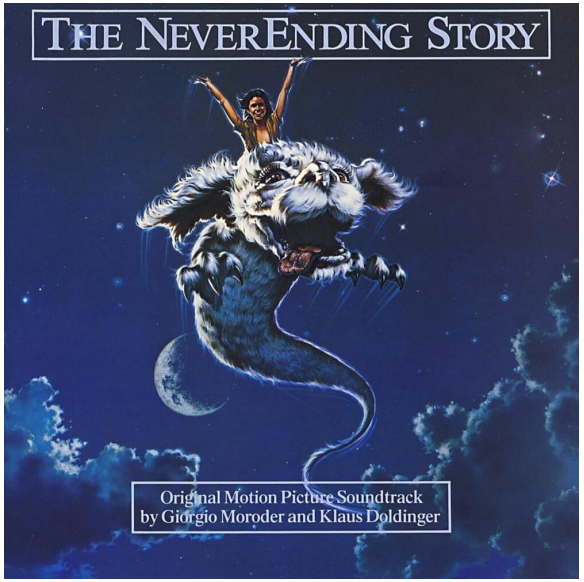




Lew TE et al., *Blood Adv*. 2021 Sep 3:. Epub ahead of print. PMID: 34478505.

Final Thoughts:

- High-risk CLL cannot be cured by CIT
- Therapeutic switch from CIT to TT to (C)IT to IT/TT
- High-risk is an evolving concept
- Decoding mechanisms of disease progression
- Decoding mechanisms of primary and acquired drug resistance



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2nd edition
Unmet challenges in high risk hematological malignancies: from benchside to clinical practice

→

3rd edition
Towards meeeting unmet challenges in high-risk CLL

Main Topics

- Targeting tumor cells
- Targeting immune cells and bystander cells
- Antibody-drug conjugates
- Bispecific antibodies
- Abscopal effect of radiotherapy
- CAR-T cells, NK, and γδ T cells
- Targeting the microbioma
- Cancer immunometabolism
- 3D cell culture models
- Mechanisms of immune resistance
- Immune lessons from allogeneic transplantation
- Tumor vaccination: back to the future

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