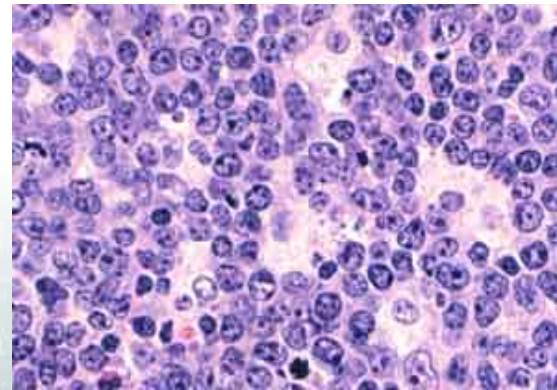
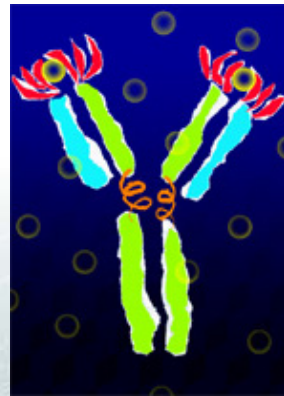




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Role of the B cell receptor in B cell oncogenesis

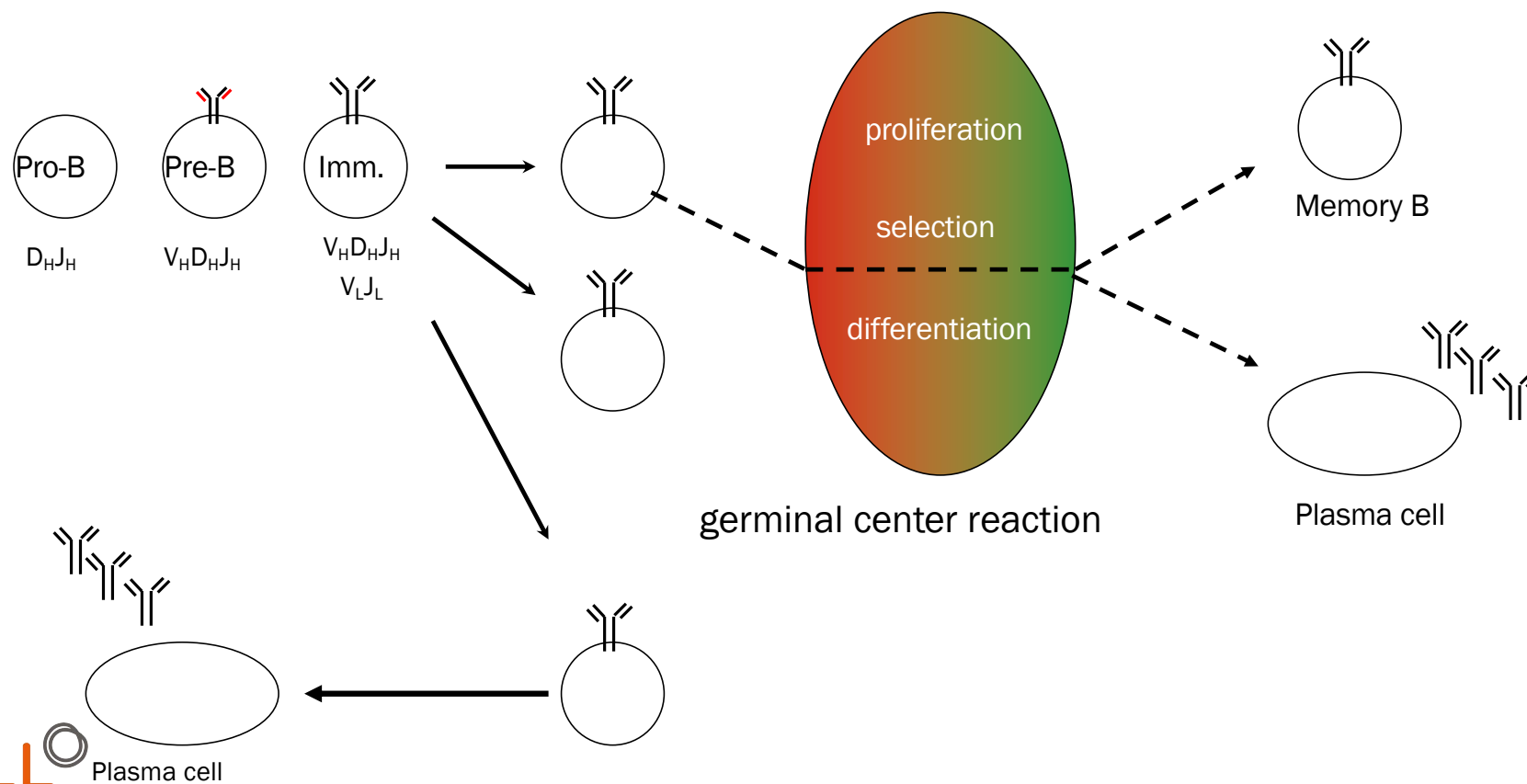


Stefano Casola, MD; PhD

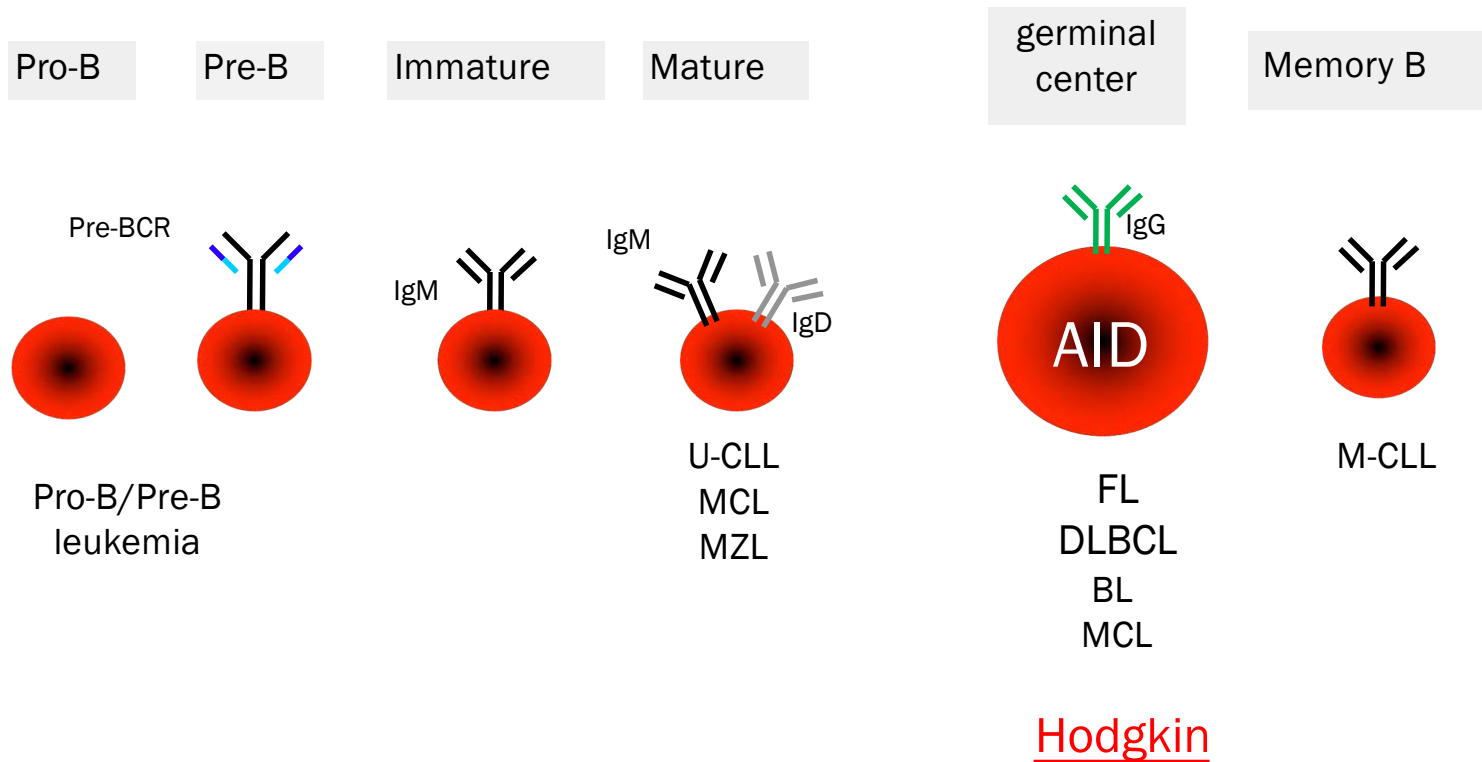


No conflicts to disclose

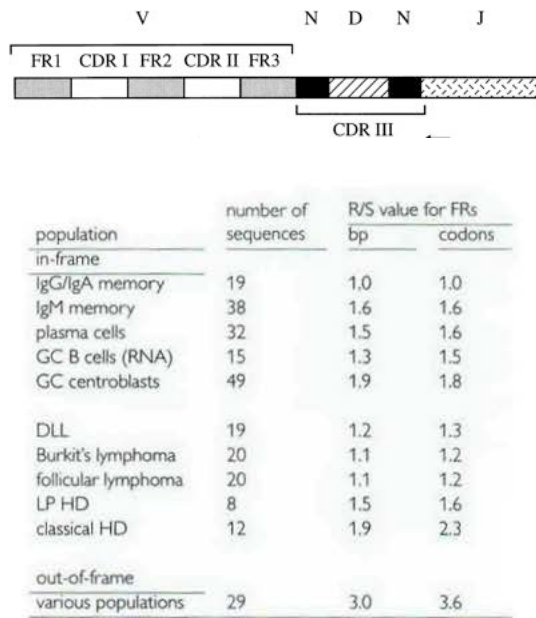
Progression through B cell development is strictly dependent on continuous expression of a functional B cell antigen receptor (BCR)



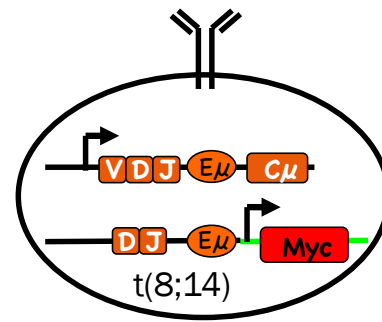
Mature B cell neoplasms conserve BCR expression



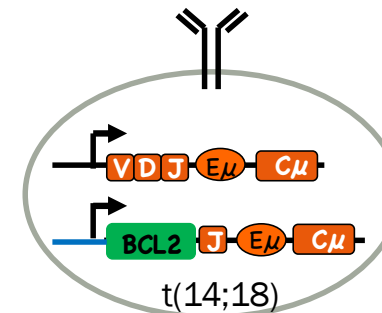
BCR importance for mature B cell neoplasms: hints from genetics



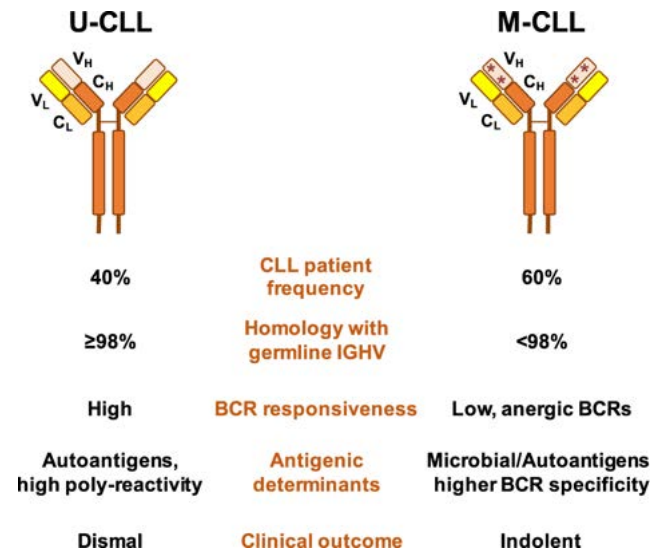
Klein et al. Immunol. Rev. 1998



Burkitt lymphoma



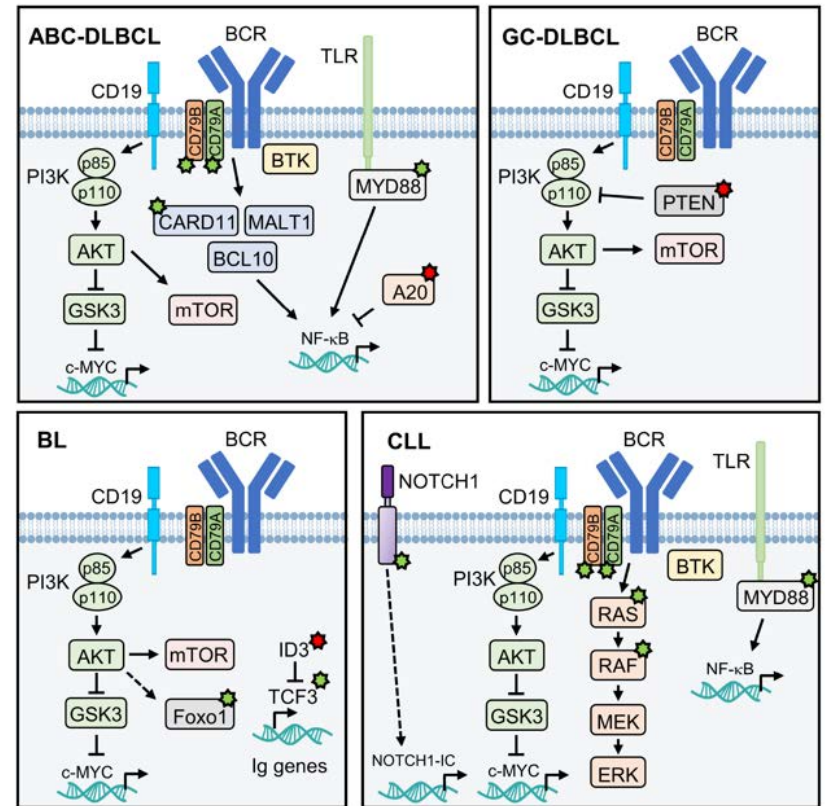
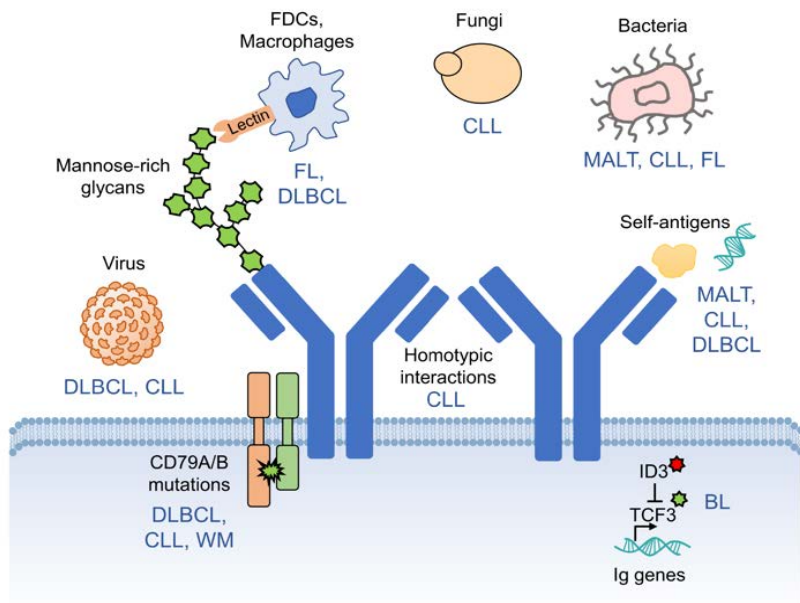
Follicular lymphoma



Ten Hacken et al., Leukemia 2019

- Stereotypic BCRs

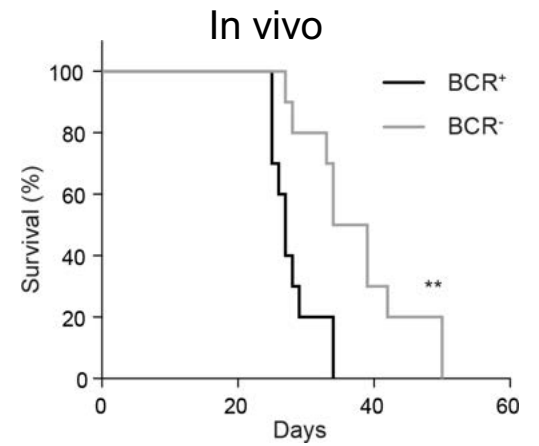
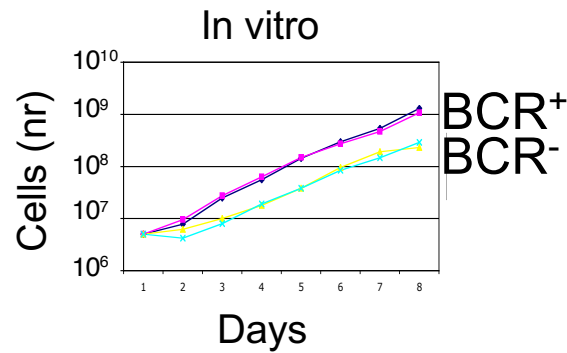
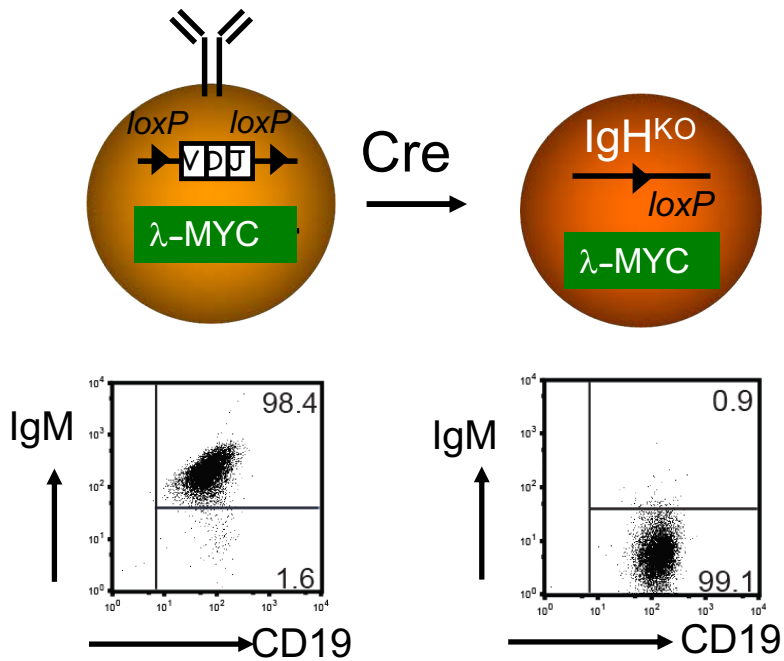
BCR activation in malignant B cells



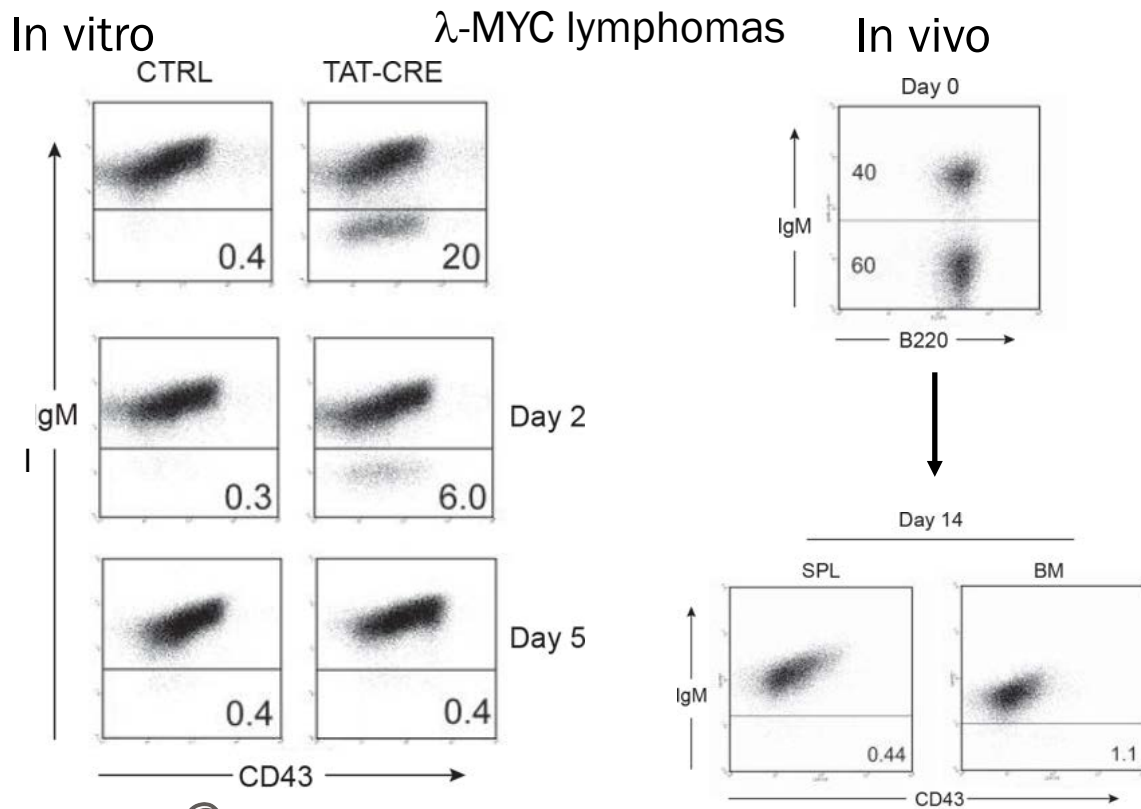
How do malignant B cells react to BCR inactivation?

BCR extinction does not prevent MYC lymphoma growth in vivo

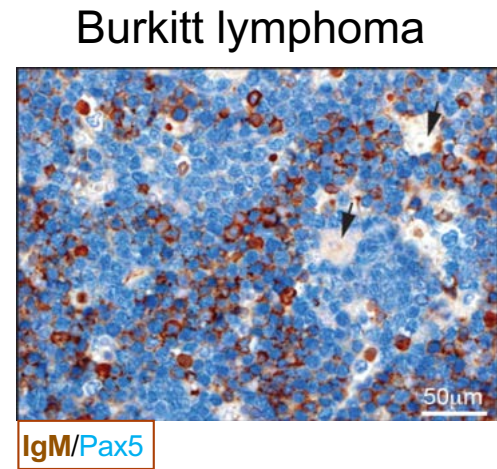
λ -MYC lymphoma



BCR enhances MYC lymphoma cell competitive fitness

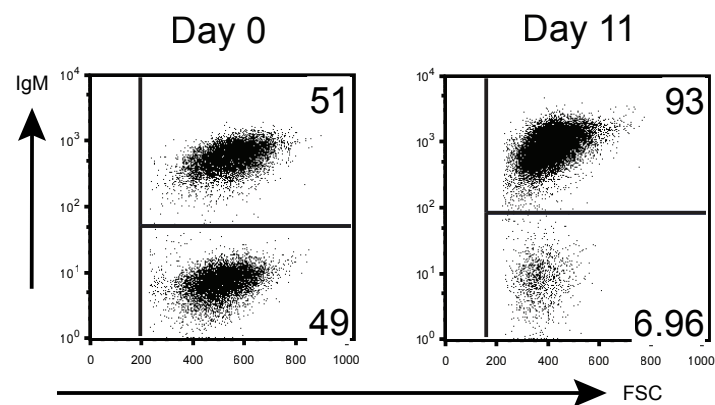


Varano et al, Nature 2017

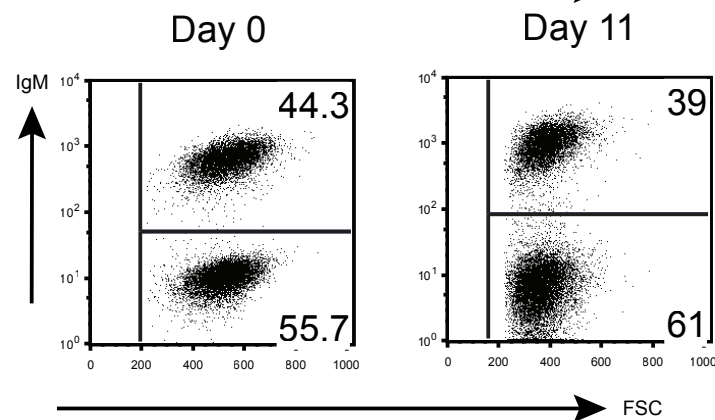


Davis, Staudt et al., Nature, 2010
 Schmitz, Staudt et al., Nature, 2012
 Cheong, Chiarle et al., Nature Commun., 2016
 Havranek et al. Blood 2017
 Phelan et al. Nature 2018

BCR-less lymphoma subclones restore optimal fitness

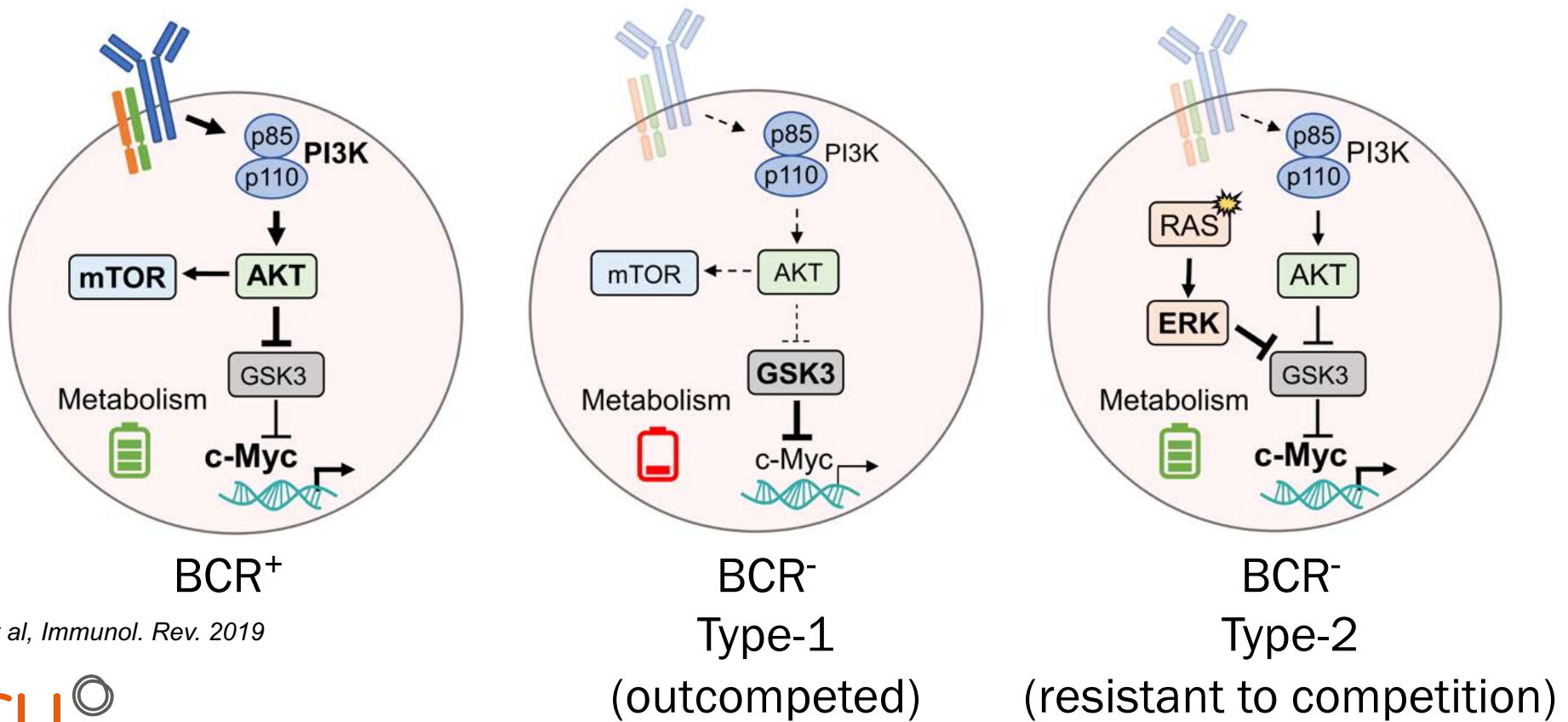


BCR dependent lymphoma



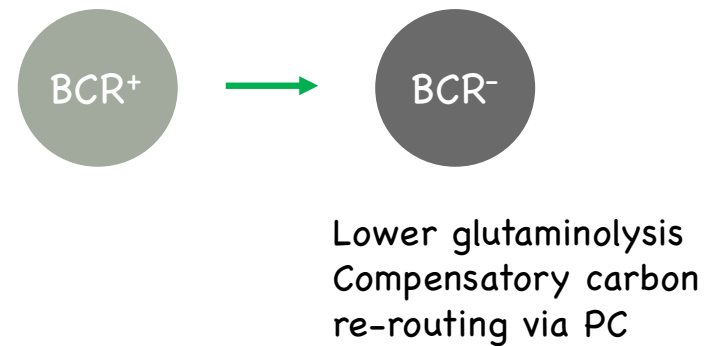
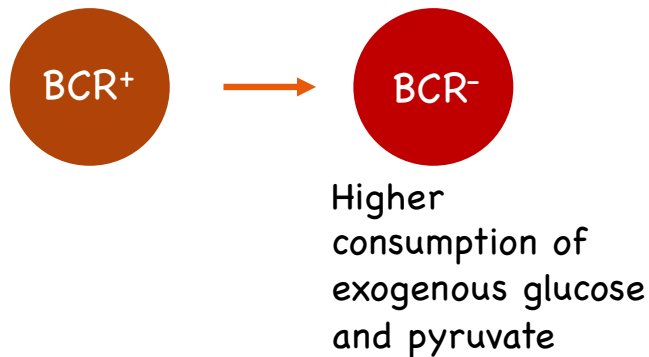
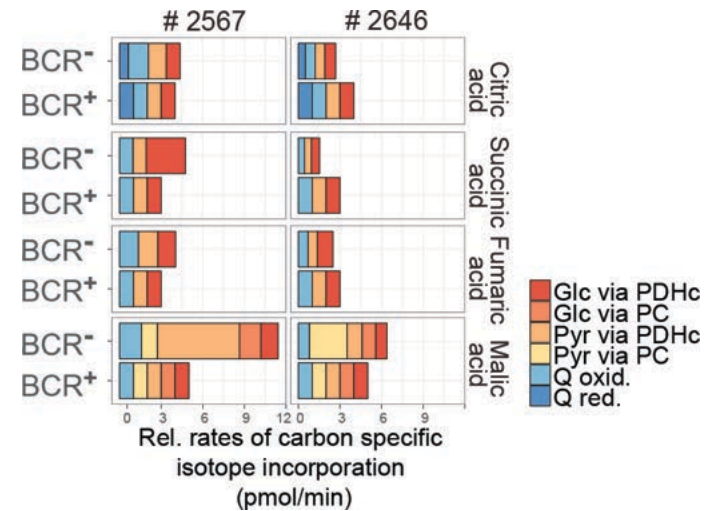
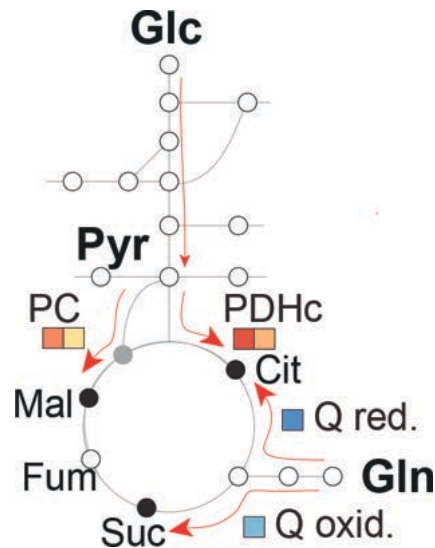
BCR independent lymphoma

The BCR signalosome controlling Myc-driven lymphoma fitness

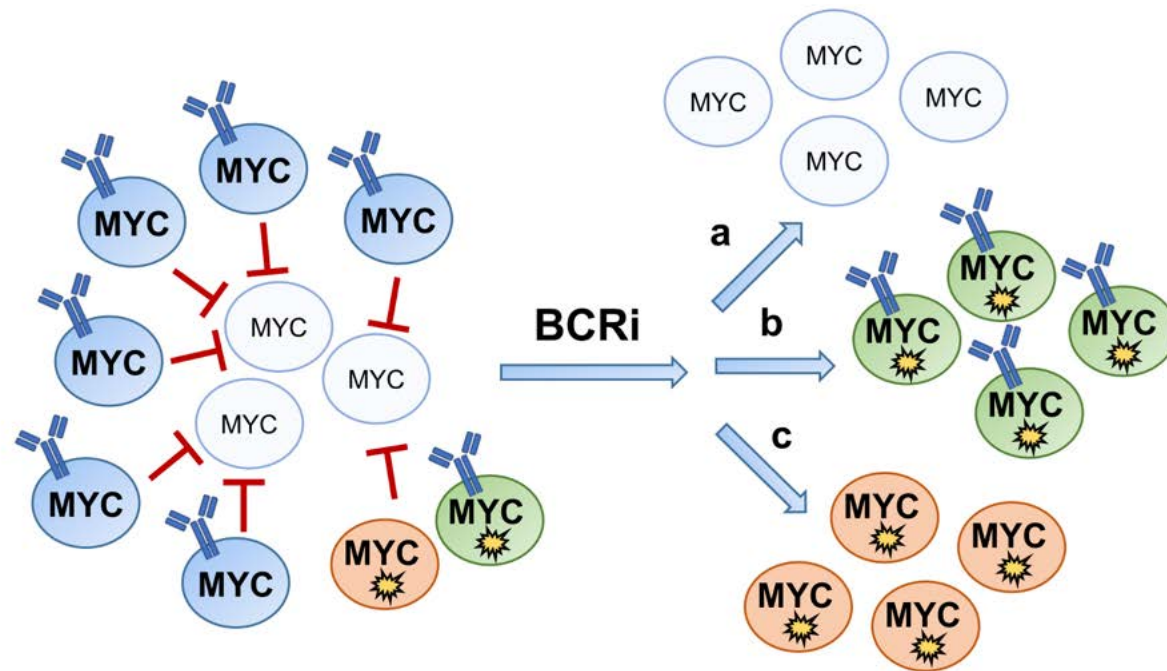


Casola et al, Immunol. Rev. 2019

Lymphoma respond to BCR loss rewiring exogenous glucose and glutamine catabolism



Possible B cell tumor evolution trajectories under anti-BCR therapies

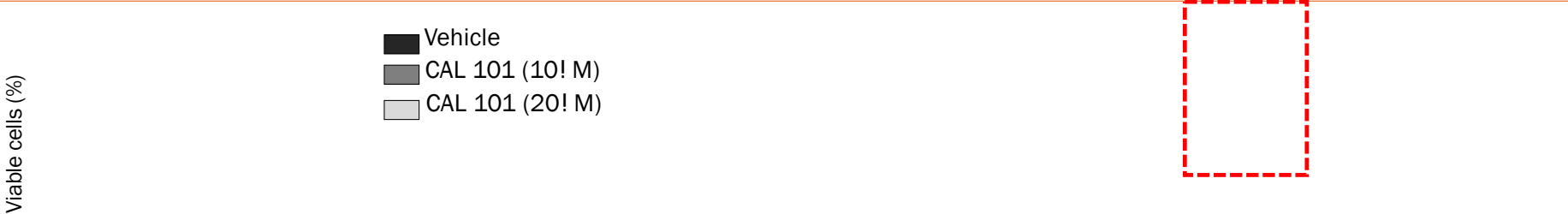


Casola et al, *Immunol. Rev.* 2019

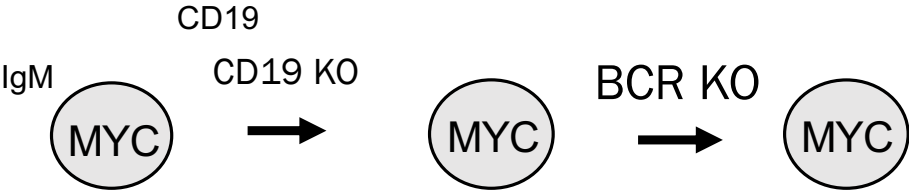
Open questions

1. How Ig-less lymphomas overcome BCR requirement for survival, and how do they evolve compared to their BCR⁺ counterparts?
2. Are distinct B cell malignancies selecting similar mechanism(s) to bypass BCR inactivation?
3. Can such knowledge help design new treatments to eradicate tumor B cells resisting BCR extinction/inhibition?

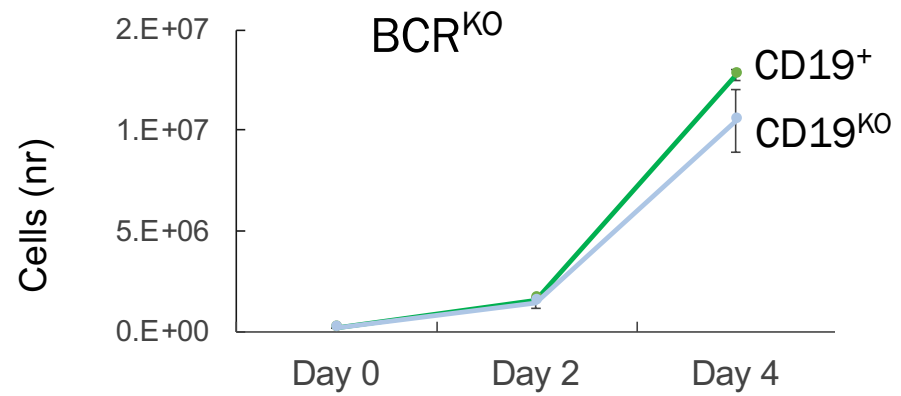
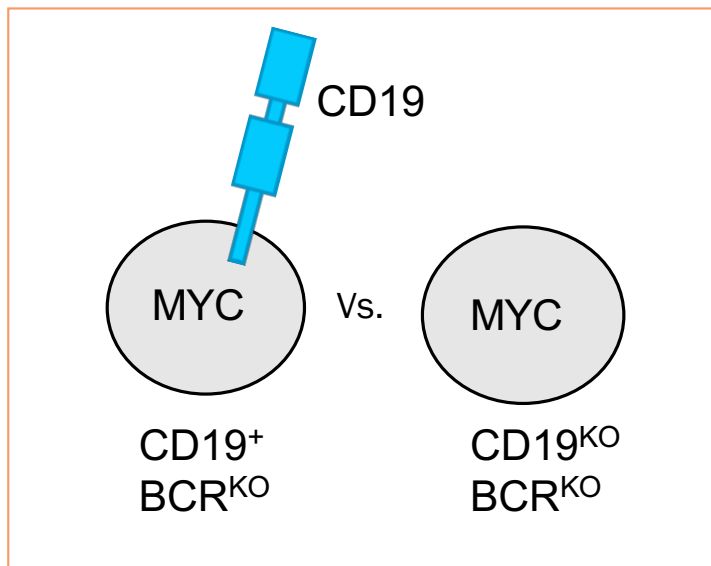
Role of the CD19/PI3K δ axis in the survival of Ig-less MYC lymphomas



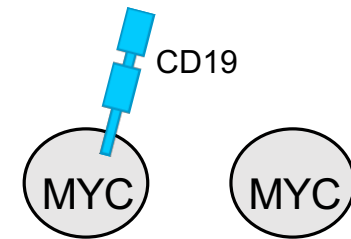
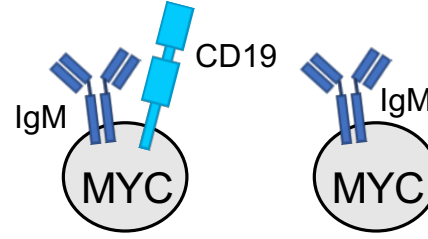
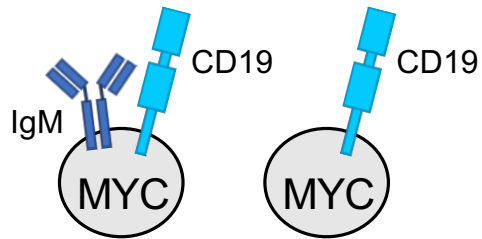
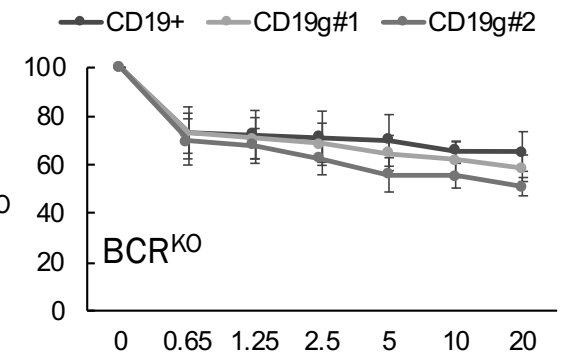
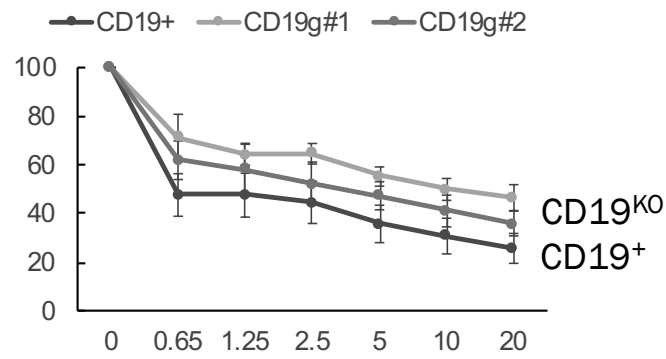
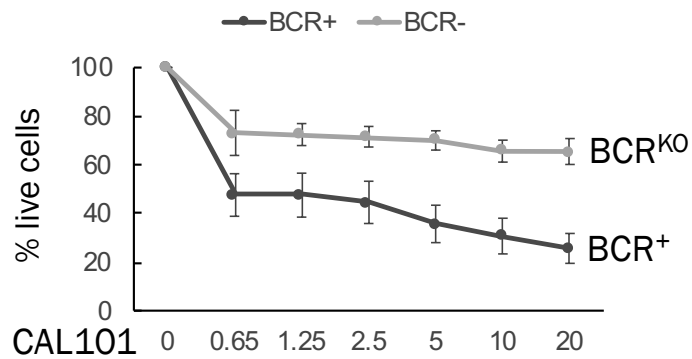
Scharenberg et al,



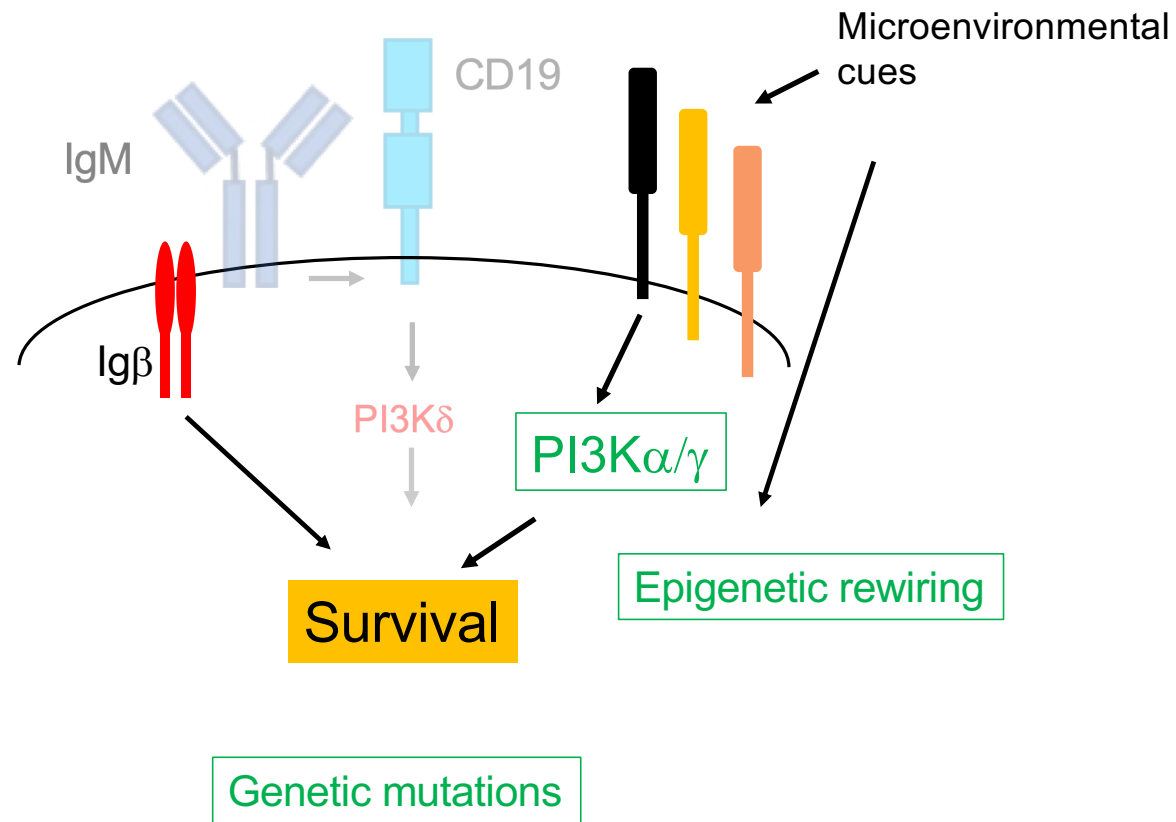
MYC lymphomas overcome combined BCR/CD19 loss



BCR/CD19 mutant lymphomas gain resistance to PI3K δ inhibition

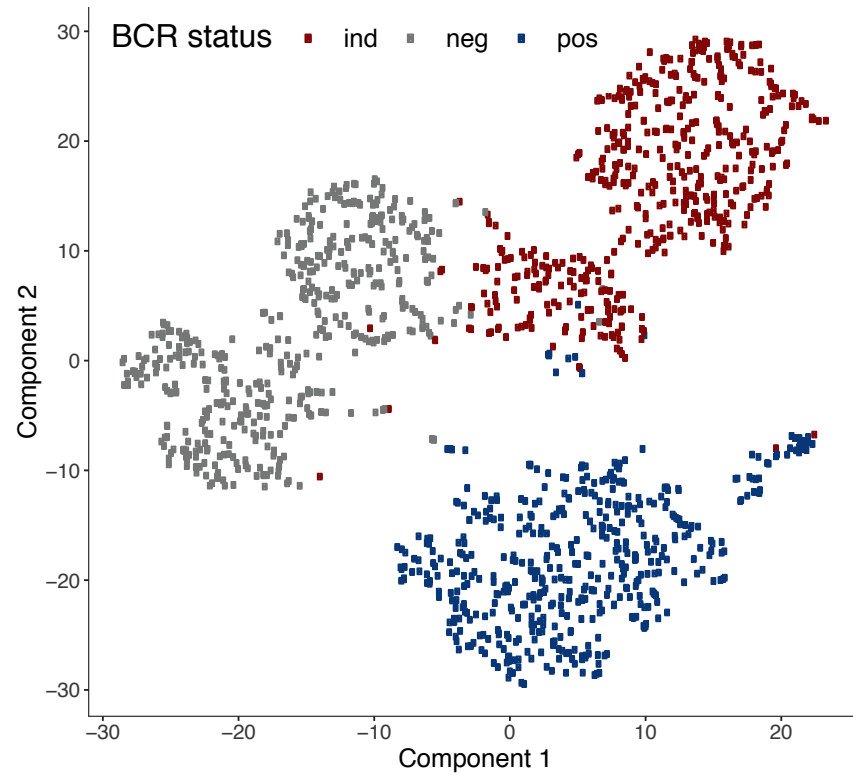
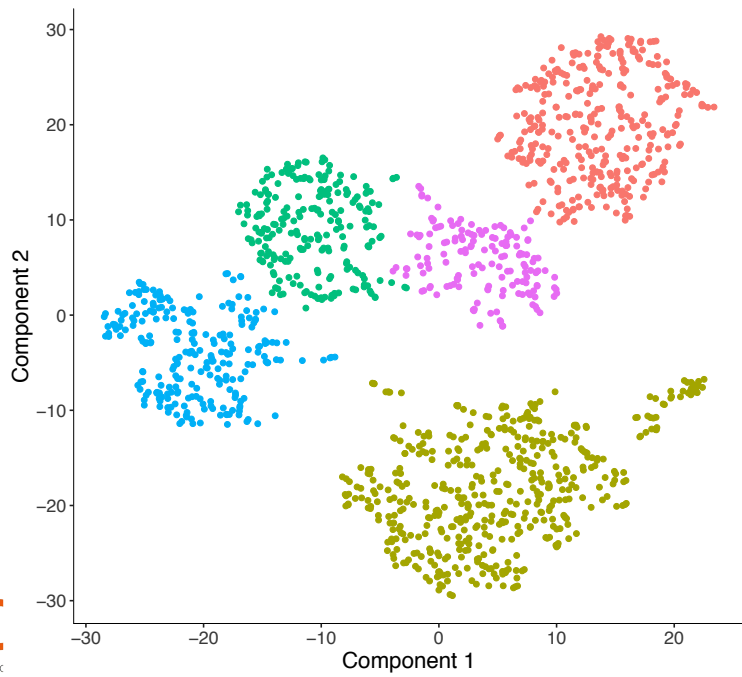


How can lymphomas bypass the BCR/CD19/PI3K δ signaling axis?

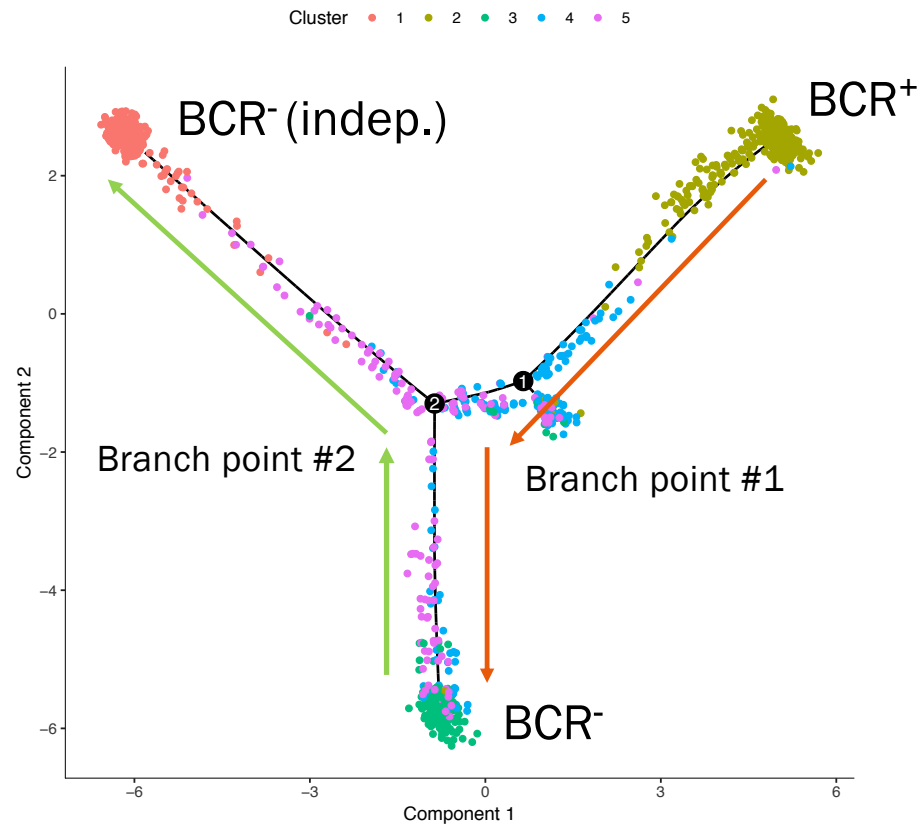
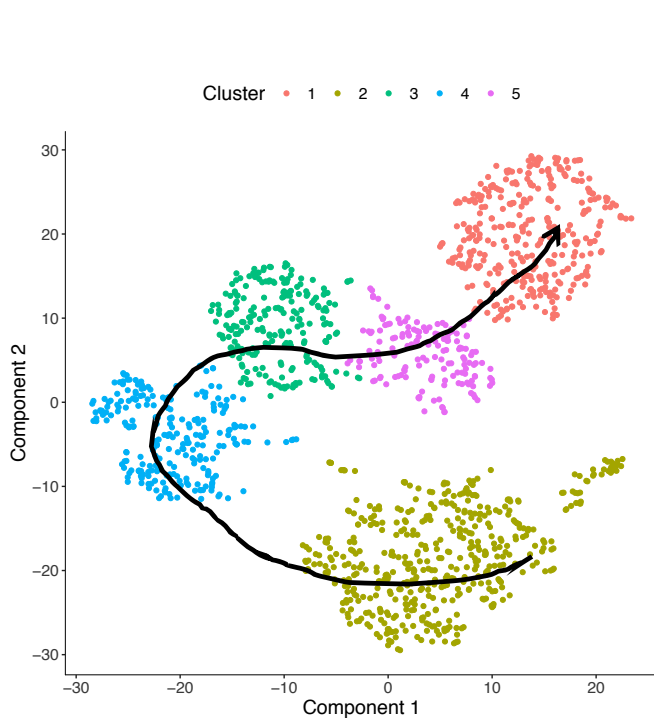


Tracking lymphoma evolution in response to BCR extinction

Single cell RNA-seq

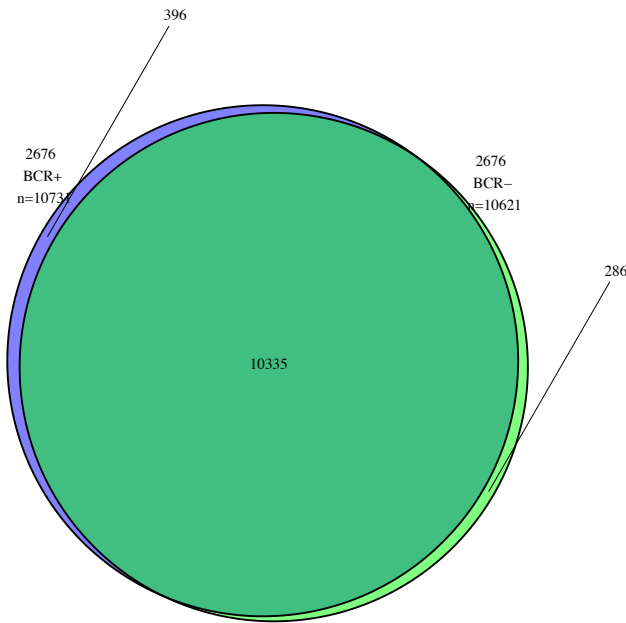


Trajectory inference of MYC lymphoma evolution following BCR inactivation

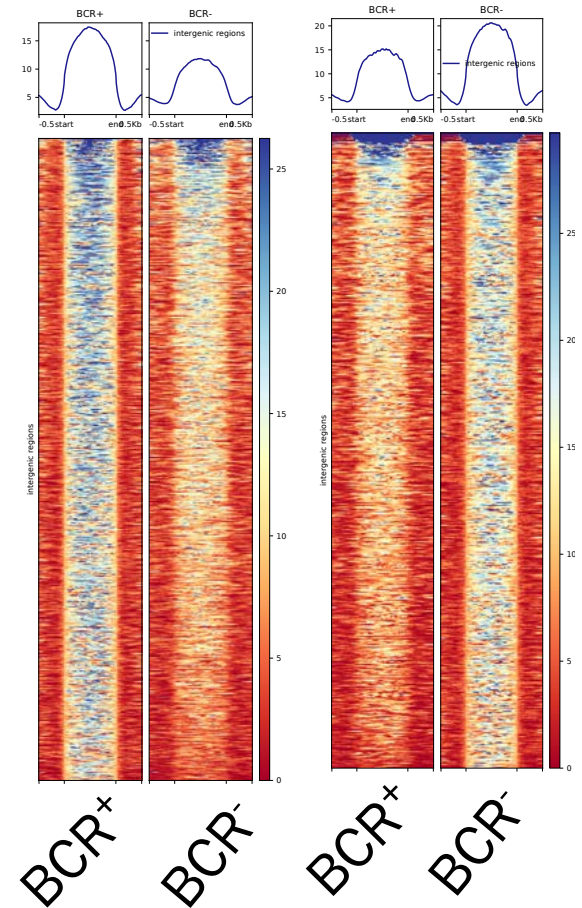
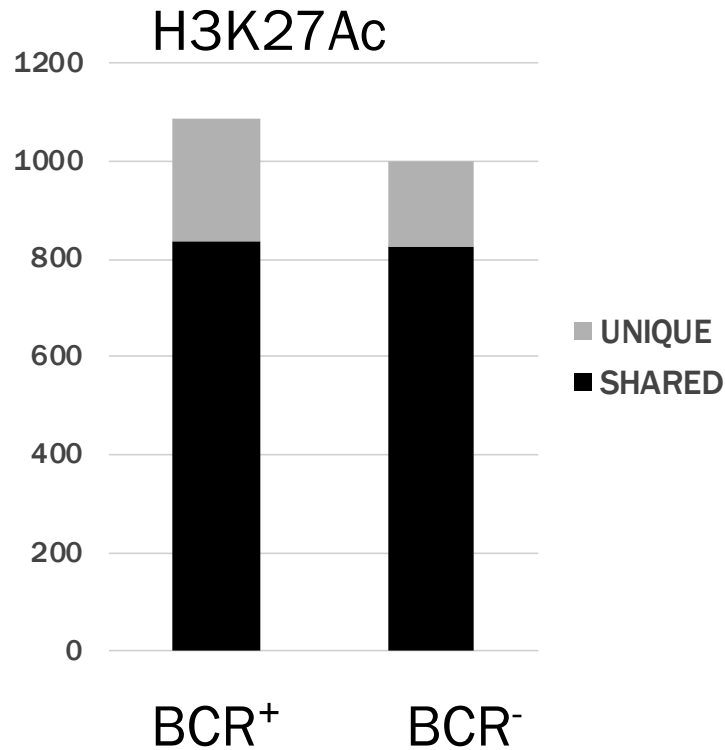


BCR regulates the epigenetic landscape of lymphoma B cells

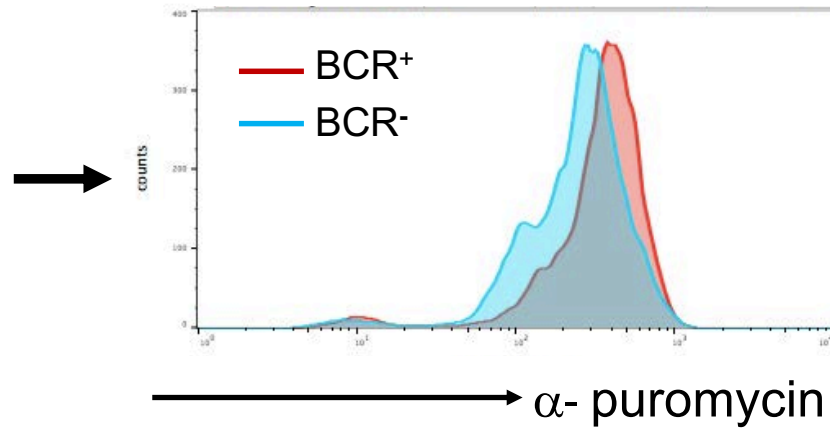
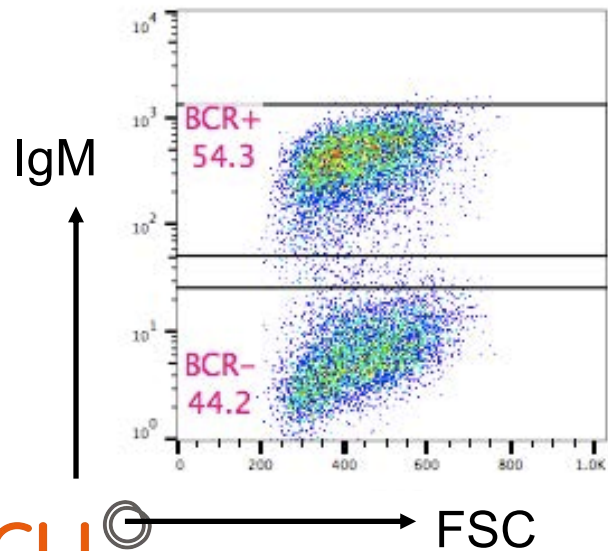
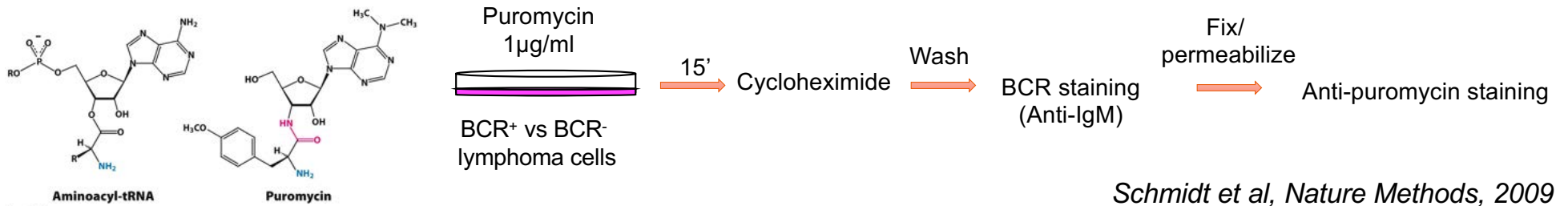
H3K27Ac (gene promoters)



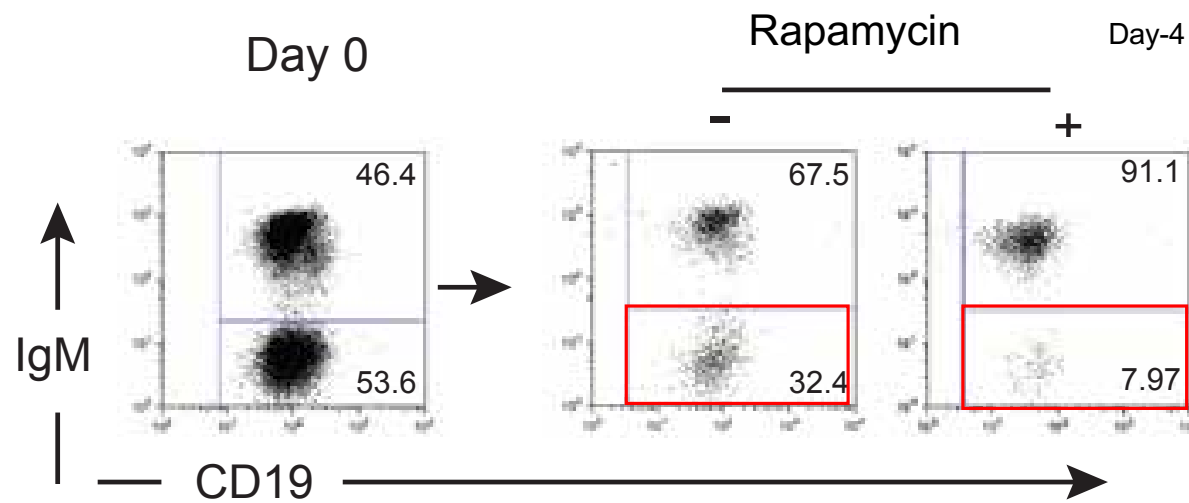
B cell enhancers (source: Phantom 5)



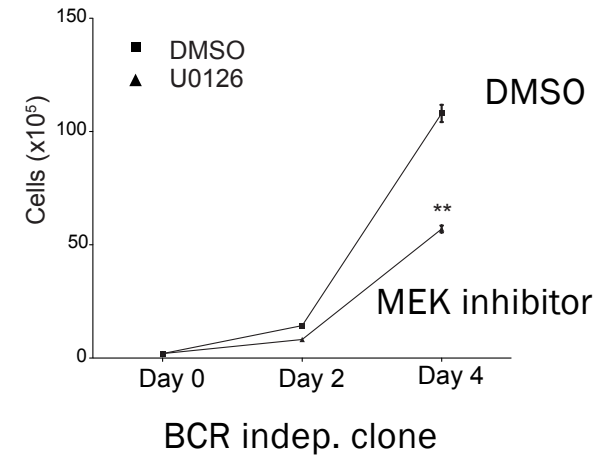
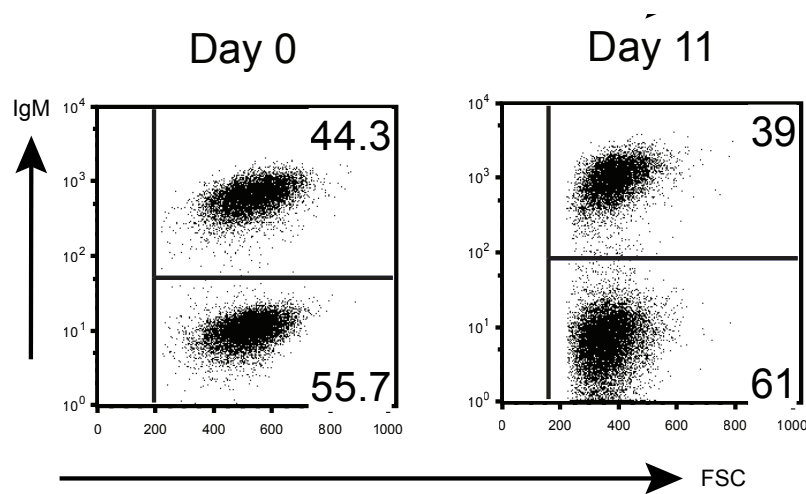
BCR loss reduces protein synthesis rate in lymphoma cells



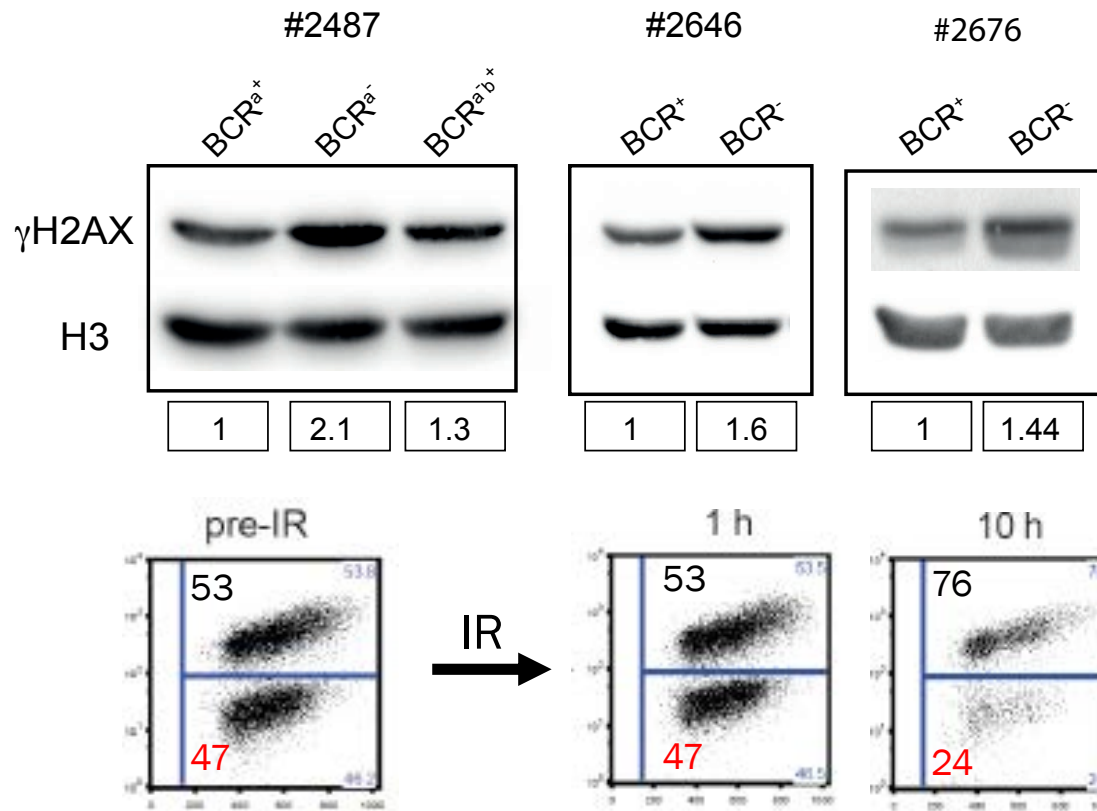
BCR-defective MYC lymphomas depend more on MTORC1 signaling



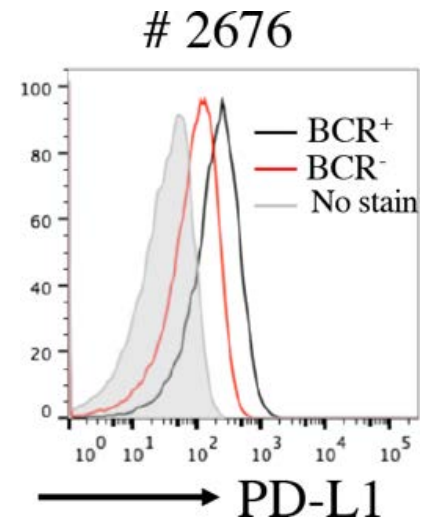
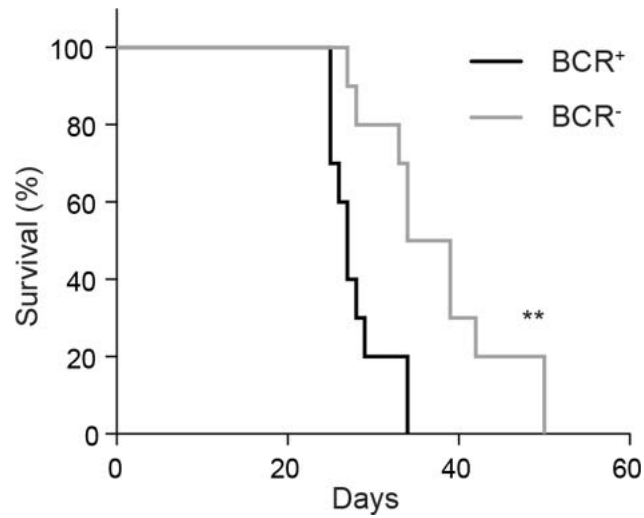
BCR-less lymphomas with chronic RAS/MAPK activation suffer from pharmacological MEK inhibition



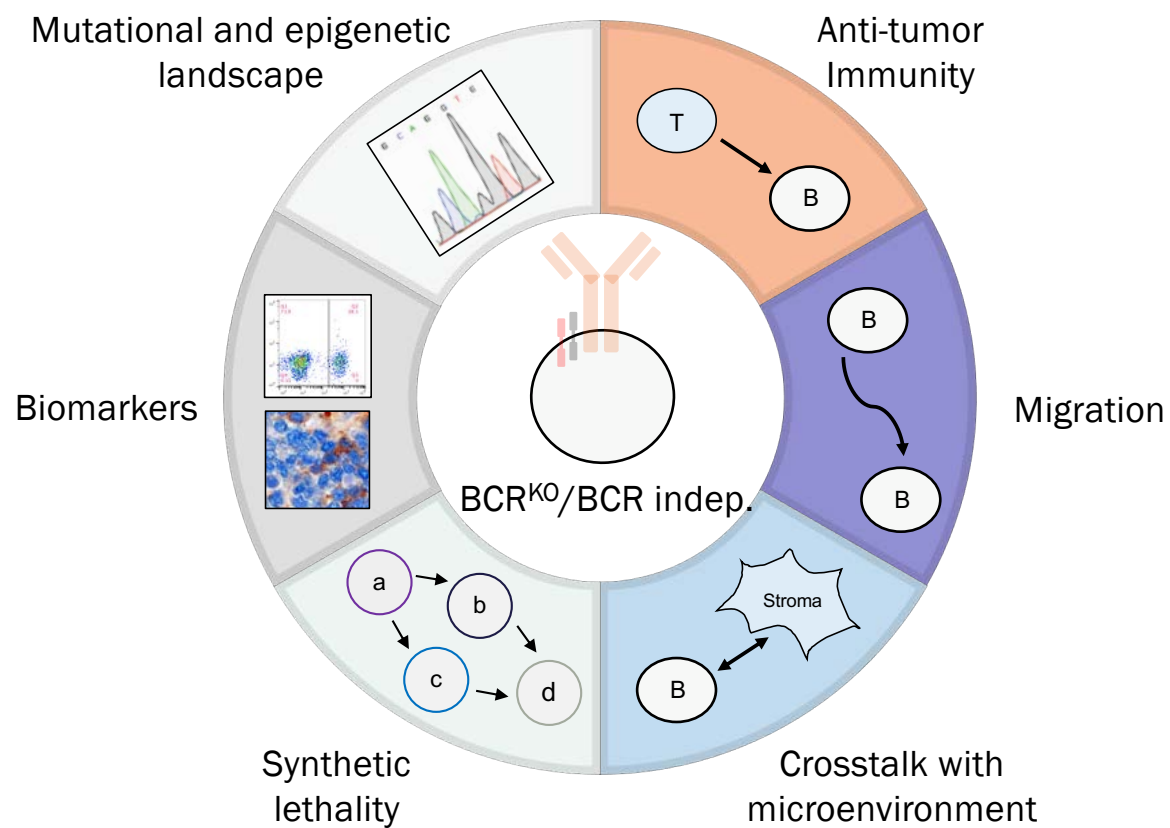
BCR inactivation enhances radiosensitivity of Myc lymphomas



Possible influence of the BCR on MYC lymphoma immunogenicity



Fighting/preventing B cell tumor resistance to BCR inhibition: the next goals



Acknowledgments



Federica La Mastra



Hiroshi Arima



Paola Sindaco



Federica Greco



Federica Zanardi

Spedali Civili, Brescia
Fabio Facchetti
Silvia Lonardi

Max Delbrueck Center, Berlin
Klaus Rajewsky

San Raffaele Hospital, Milan
Maurilio Ponzoni

Stefan Kempa
Christin Zazada

Universita' di Palermo
Claudio Tripodo

University of Kiel
Reiner Siebert
Andrea Haake



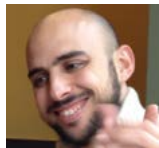
Federica Mainoldi



Martina Sormani



Daniel Garzon



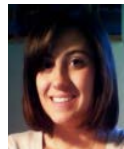
Gabriele Varano



Laura Perucho Aznar



Valentina Petrocelli



Marianna Ossorio



Simon Raffel

Single cell transcriptional signatures discriminating specific transitions of Myc lymphoma evolution following BCR loss

