

A nighttime photograph of a river scene, likely in Cambridge. A stone bridge with two arches spans the river in the background. In the foreground, several wooden rowing boats are docked along the right bank. A person is visible in a small boat on the water. The scene is illuminated by warm, golden lights, possibly from street lamps or building lights, creating a serene atmosphere. The text is overlaid on the image in white.

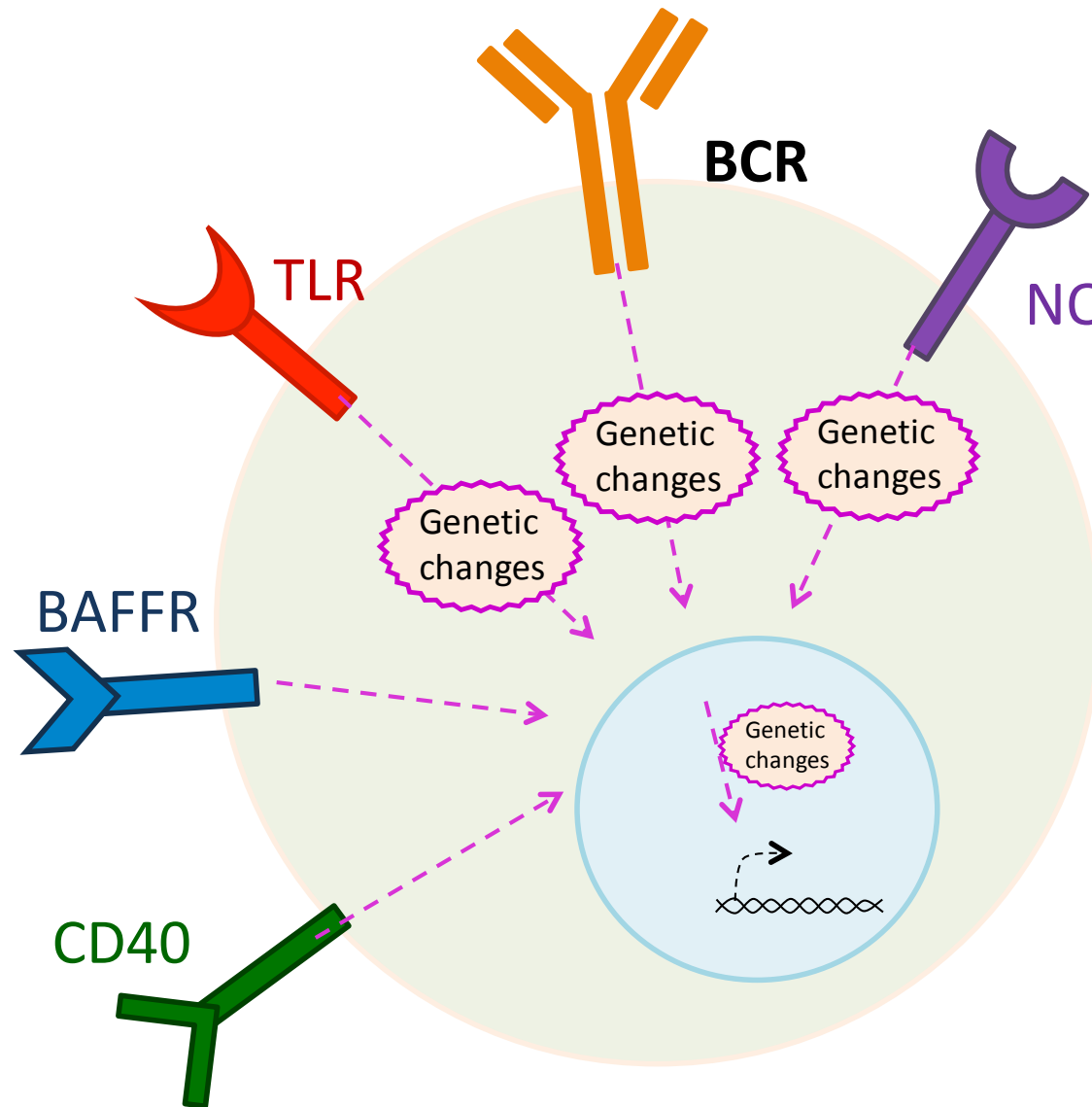
Marginal Zone Lymphoma

Somatic mutations and mechanisms

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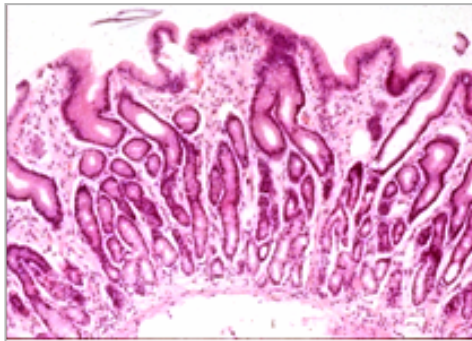
Signalling in Marginal Zone B-cells



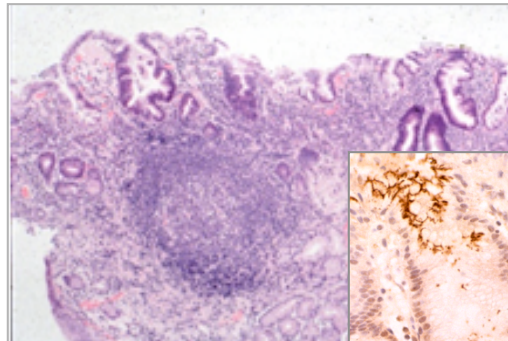
- Immunological stimulations
- genetic changes
- oncogenic cooperation

MALT lymphoma concept

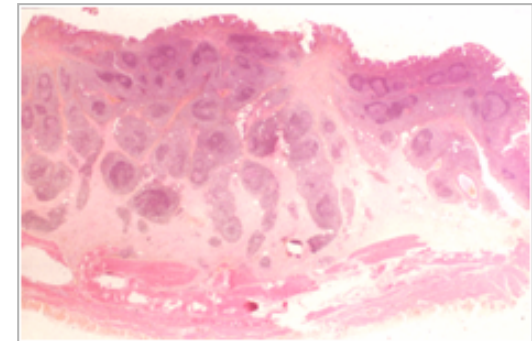
Mucosal sites
without native MALT



Chronic
inflammatory disorders

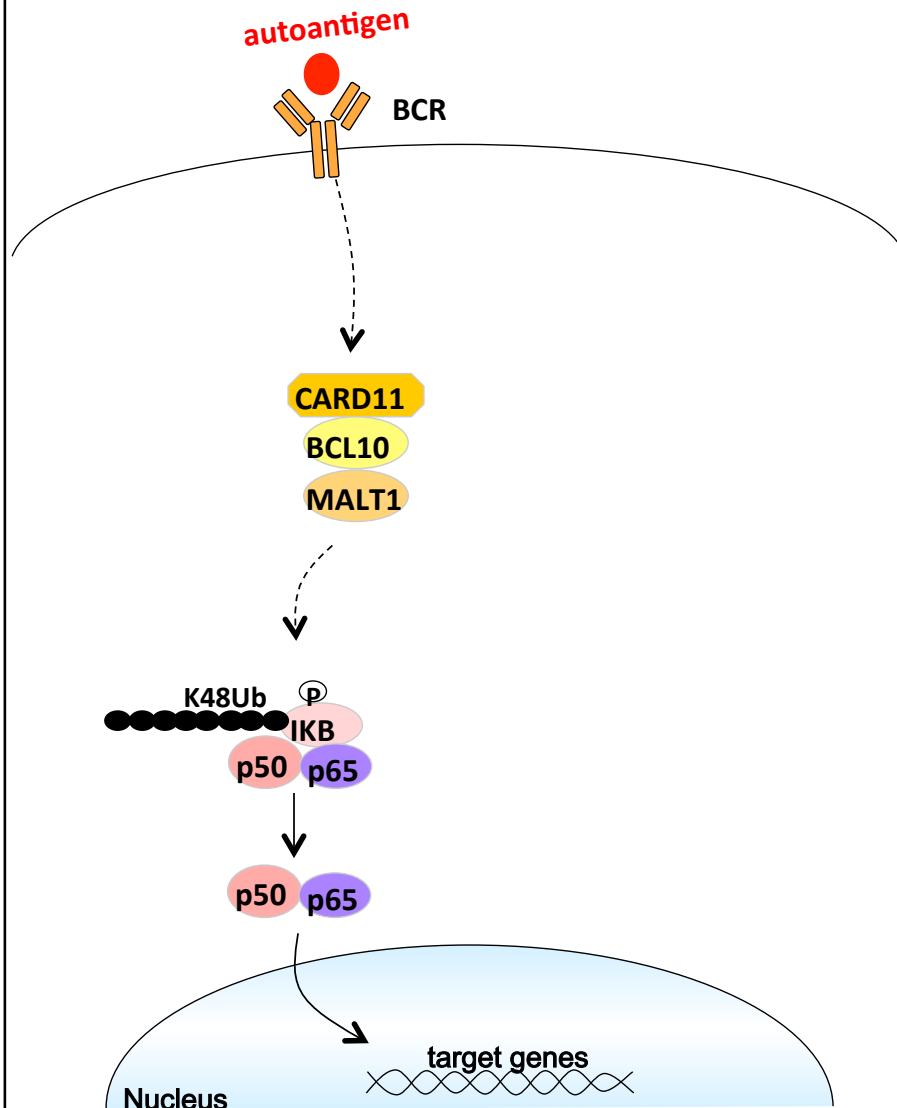


Low grade
MALT lymphoma



| MALT lymphoma | Aetiology | | Response to anti- microbial therapy |
|-----------------|------------------------|------------|-------------------------------------|
| Stomach | H pylori | ~95% | CR in ~70% |
| Skin | Borrelia burgdorferi | some | CR in case report |
| Ocular adnexa | Chlamydia psittaci | variable | CR in ~20%; PR in ~55% |
| Lung | A Xyloxidans | variable | |
| IPSID | Campylobacter jejuni | variable | CR in case report |
| Salivary glands | Sjogren's syndrome/HCV | every case | |
| Thyroid | Hashimoto thyroiditis | every case | |
| SMZL | HCV | variable | ORR in ~50% |
| NMZL | HCV | variable | CR in ~70% |

Antigenic stimulation: BCR signalling



- Surface IgM+
- Proliferate upon cross-linking slg.
- Hyper-somatic and ongoing mutations in IGH / IGL.
- Tumour Igs from gastric MALT lymphoma do not recognising H pylori antigen, but polyreactive to auto-antigens.

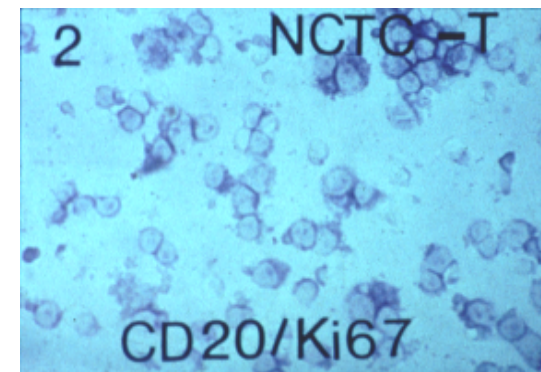
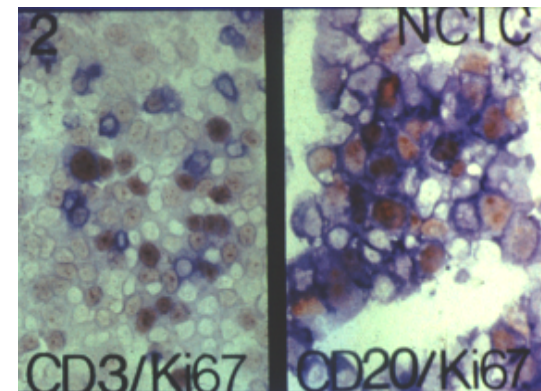
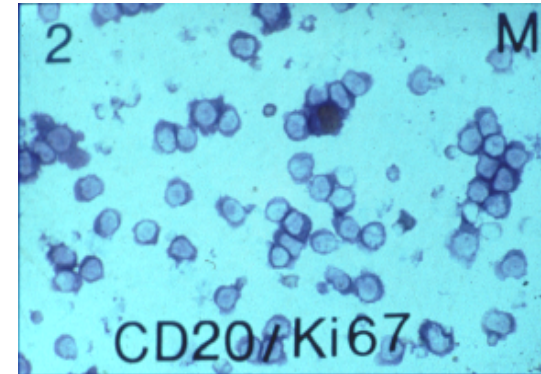
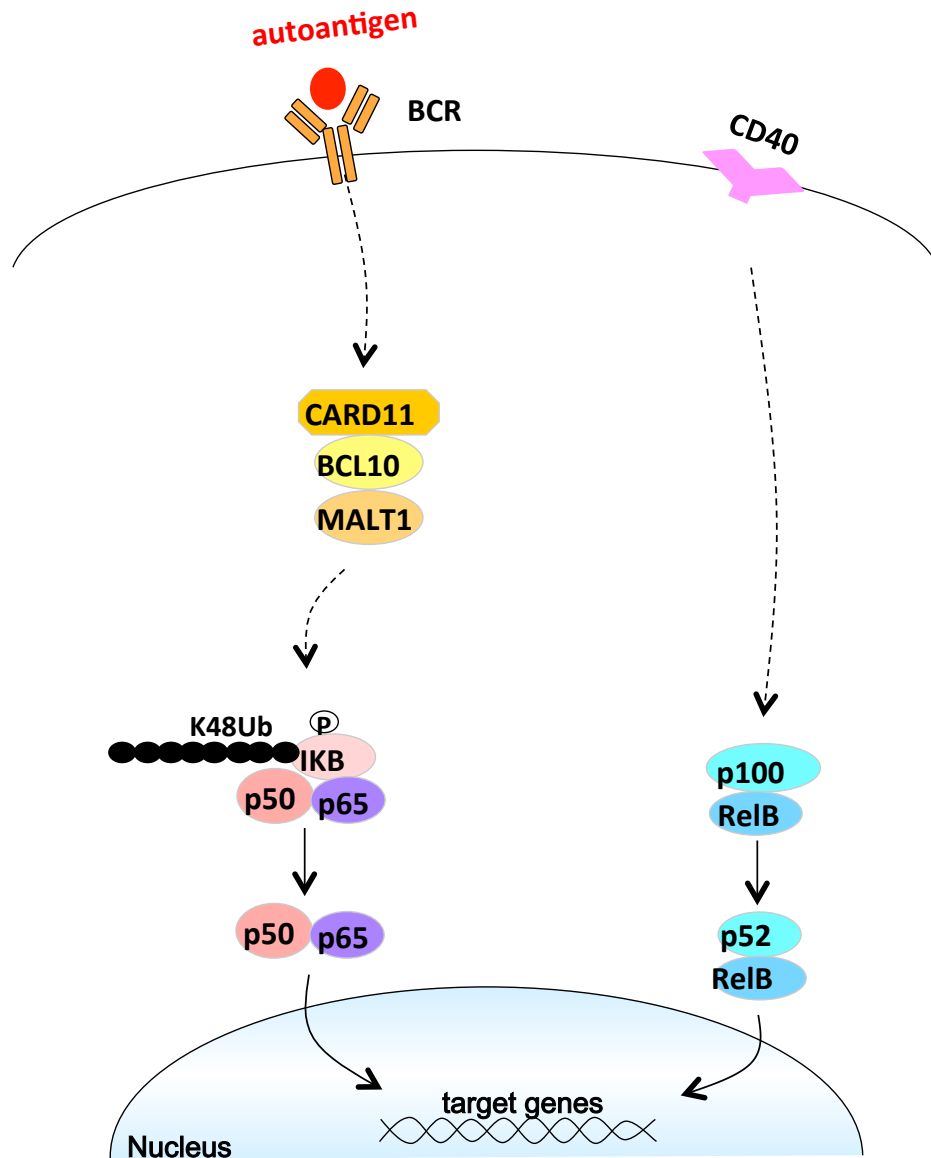
Hussell et al, J Pathol 1993
Du et al Leukaemia 1996 & Blood 1996
Hussell et al Am J Pathol 1993
Craig et al Blood 2010)

Biased IG gene usage in MALT lymphoma

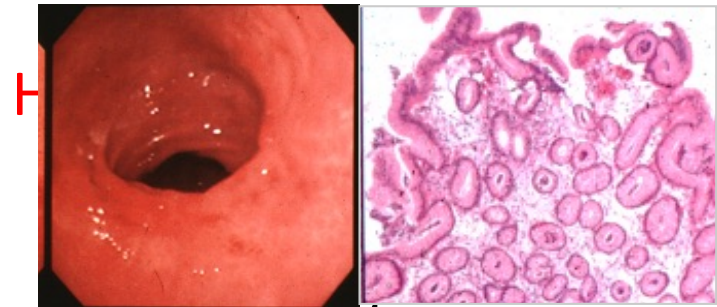
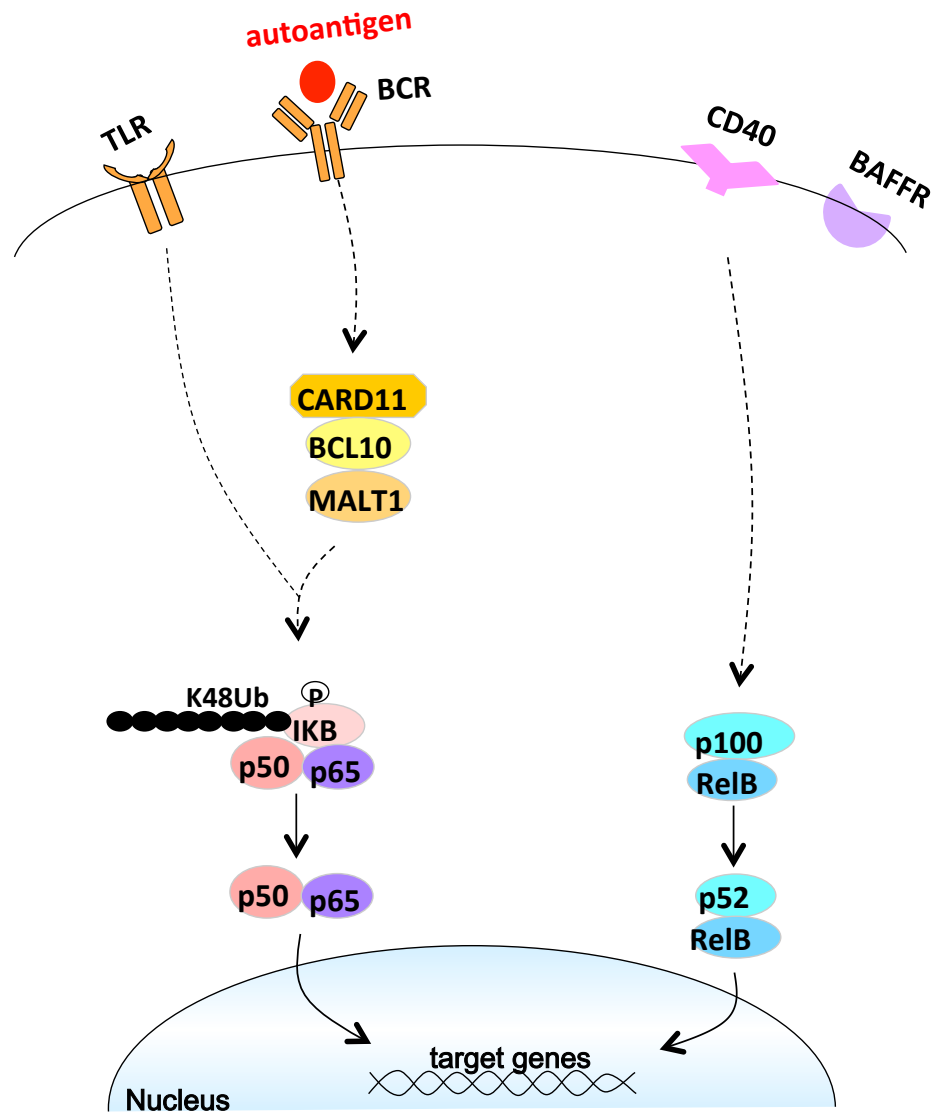
| MALT lymphoma | Biased IG gene usage | Known IG properties |
|-----------------|--------------------------|---|
| Stomach | IGHV3-7 IGHV1-69 | - rheumatoid factors |
| Salivary glands | IGHV1-69/IGKV3-20 (~50%) | - self-polyreactive |
| Ocular adnexa | IGHV4-34/IGK3-20 (~30%) | - binds to N-acetyl-lactosamine - polyreactive |
| Thyroid | IGHV3-30? | - self-polyreactive |

| | Sample | V Gene | J Gene | CDR3 Length | CDR3 sequence |
|--------------------------|------------|----------|--------|-------------|---|
| RF | RF-112/113 | IGHV1-69 | JH4 | 13 | E G R S S D Y S N P F D Y |
| | RF-BOR | IGHV1-69 | JH4 | 12 | E G R R M A I - N P F D Y |
| Salivary gland MALT-L | SA_002 | IGHV1-69 | JH4 | 12 | E G Q Q M S T - N P F D F |
| | SA_006 | IGHV1-69 | JH4 | 13 | E G K A T V T T N P F D Y |
| | SA_010 | IGHV1-69 | JH4 | 12 | E G R Q M P T - N P F D Y |
| | SA_6T | IGHV1-69 | JH4 | 13 | E G K S S D Y S N P F D Y |
| | D26010 | IGHV1-69 | JH4 | 12 | E G R Q T V T - N P F D Y |

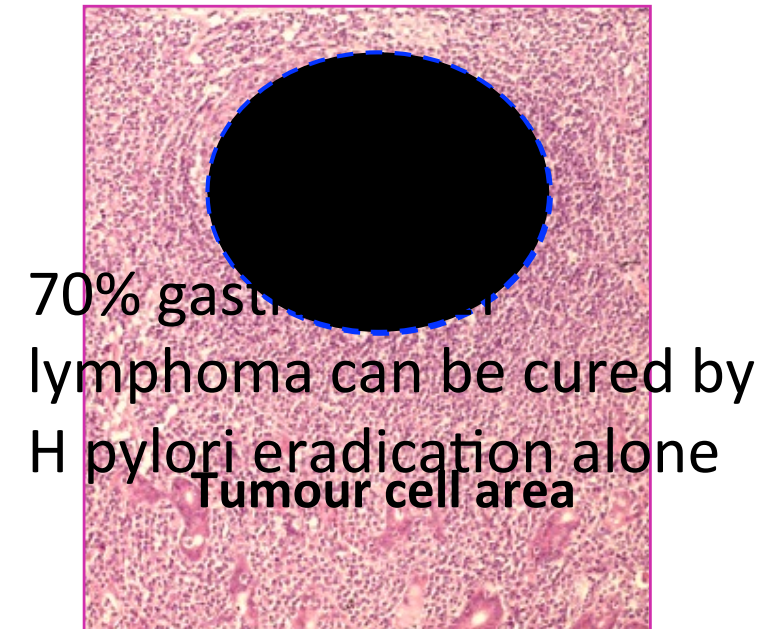
Antigenic stimulation: T cell help



H pylori eradication: assumed effect

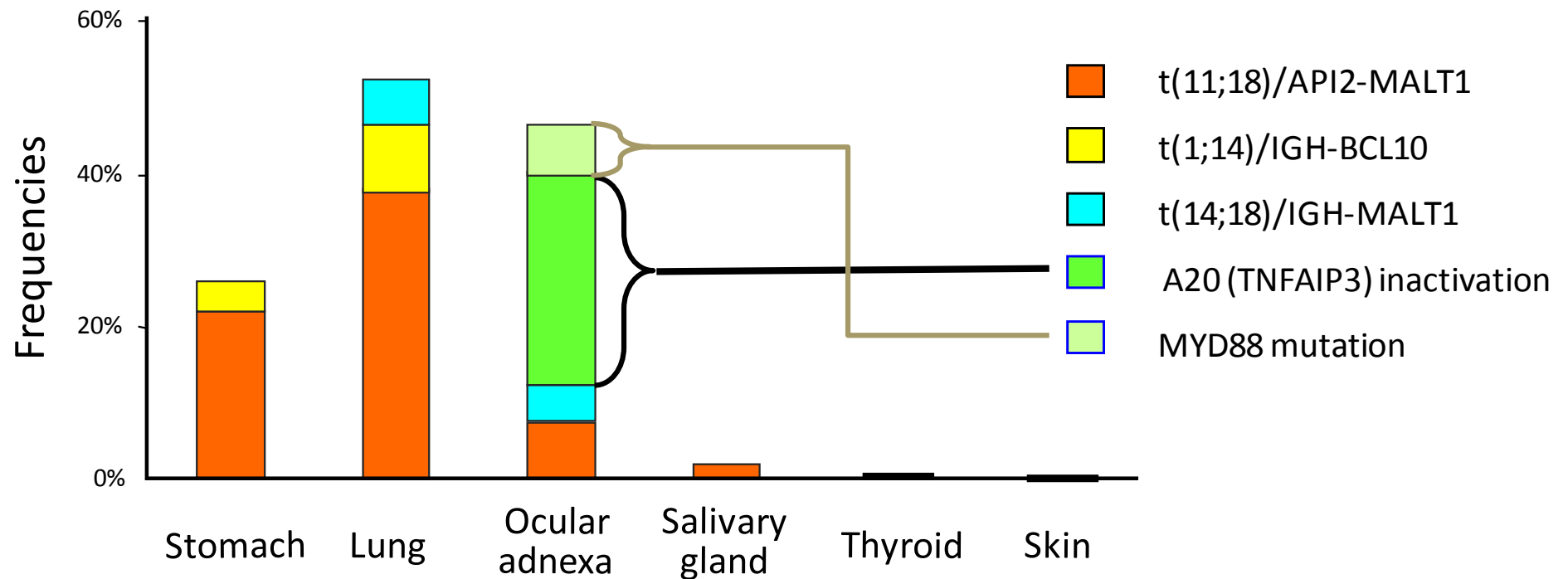


- cytokines/soluble ligands
?Other B-cell help signals



70% gastric lymphoma can be cured by H pylori eradication alone
Tumour cell area

Genetic changes in MALT lymphoma

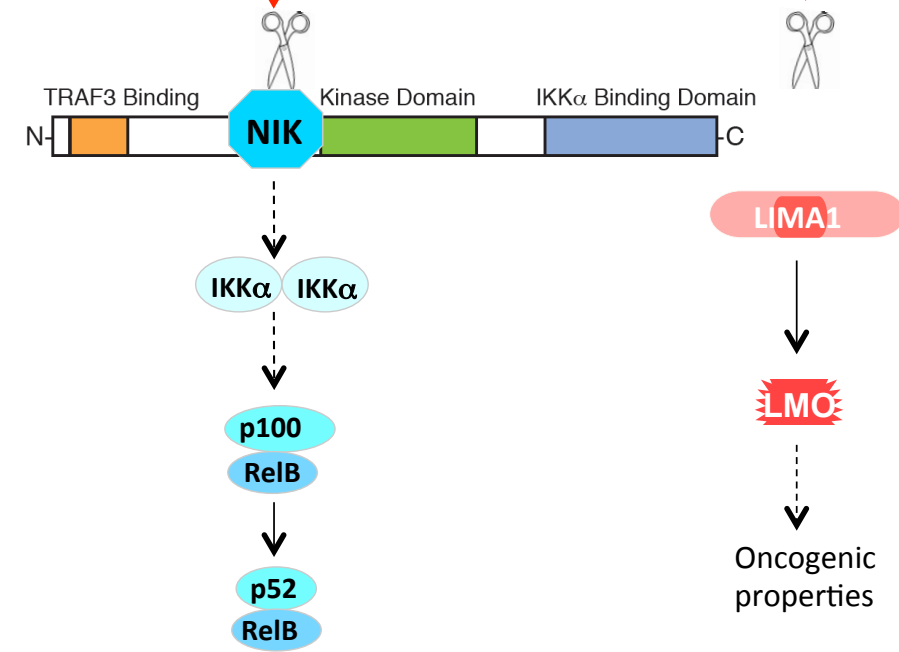
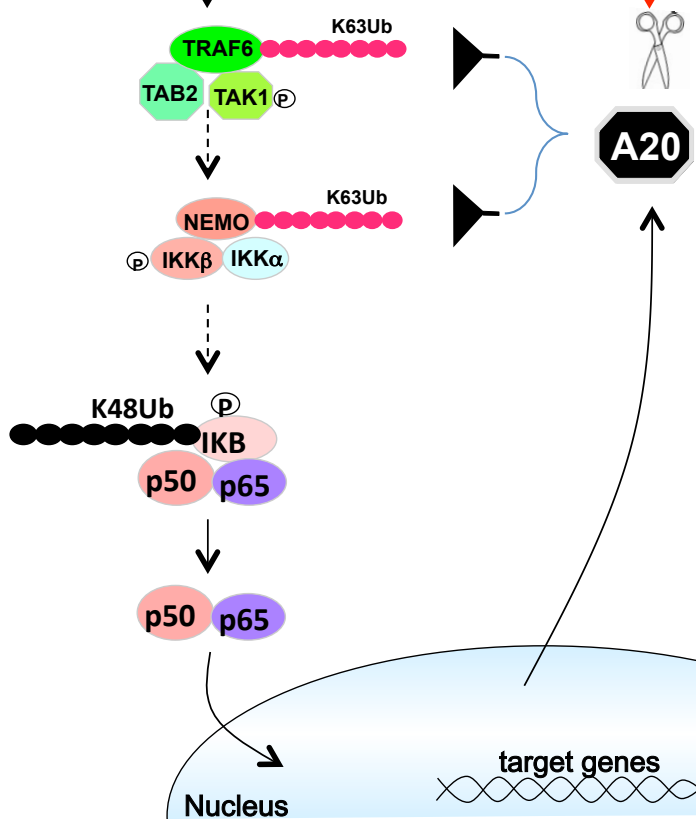
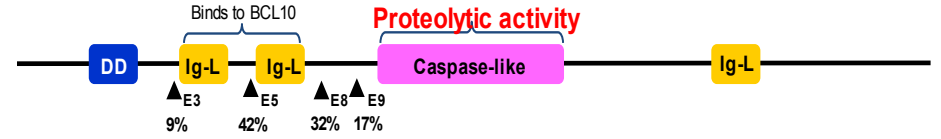
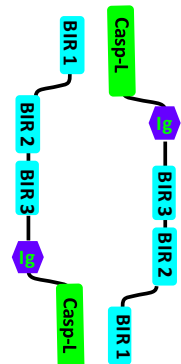
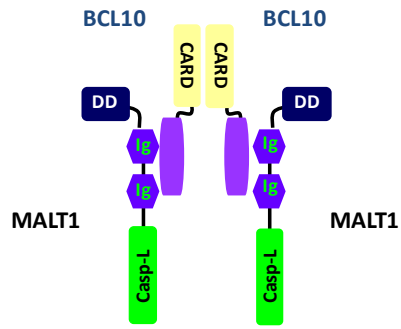


Liu et al, Gastroenterology 2002,
Ye at al, Blood 2001, 2003,
Ye at al, J Pathol 2005,
Goatly et al Modern Pathol 2008
Chanudet et al, Leukaemia 2010
Bi et al, Haematologica 2012

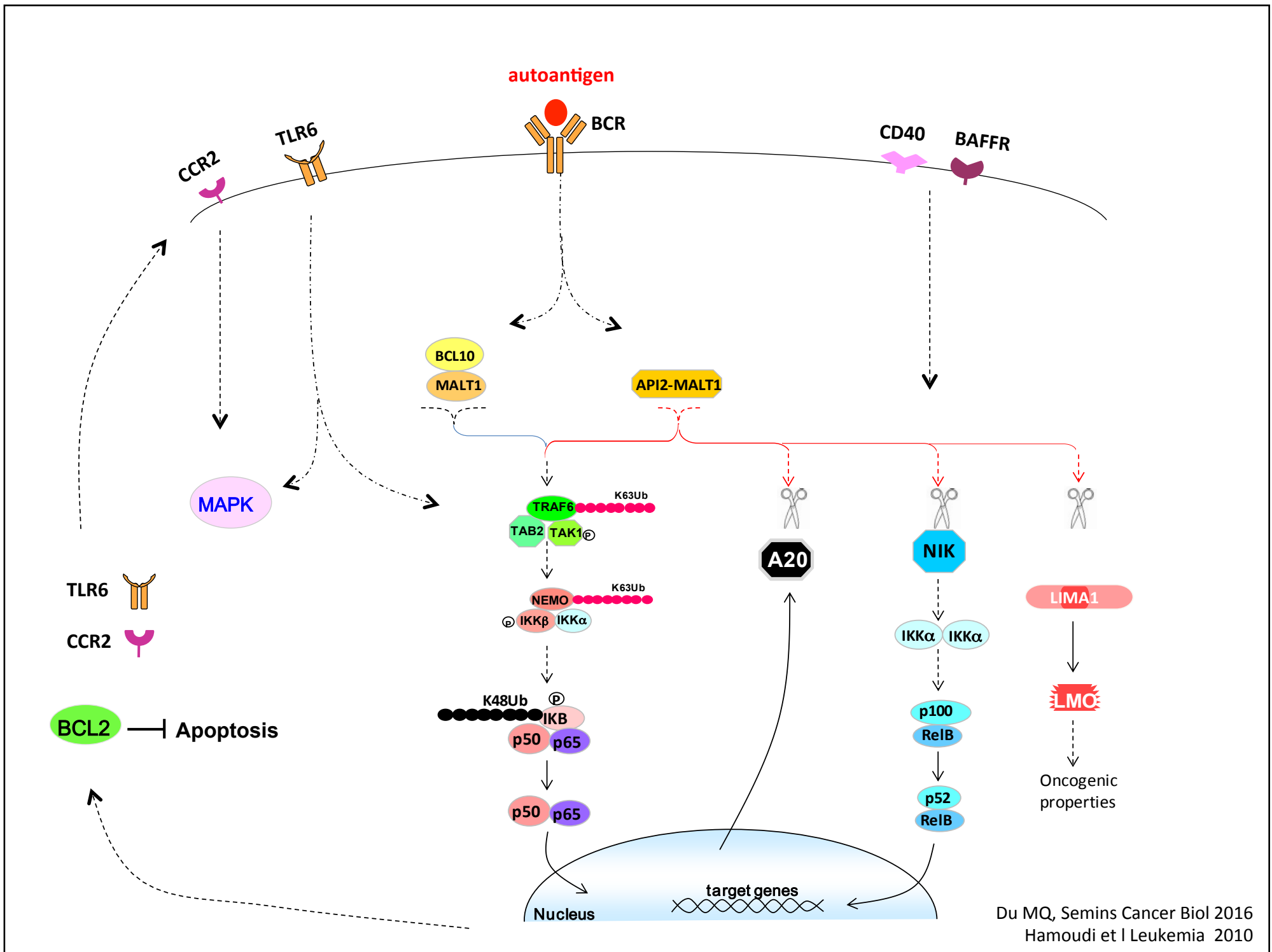
t(1;14)
IGH-BCL10

t(14;18)
IGH-MALT1

t(11;18)
API2-MALT1



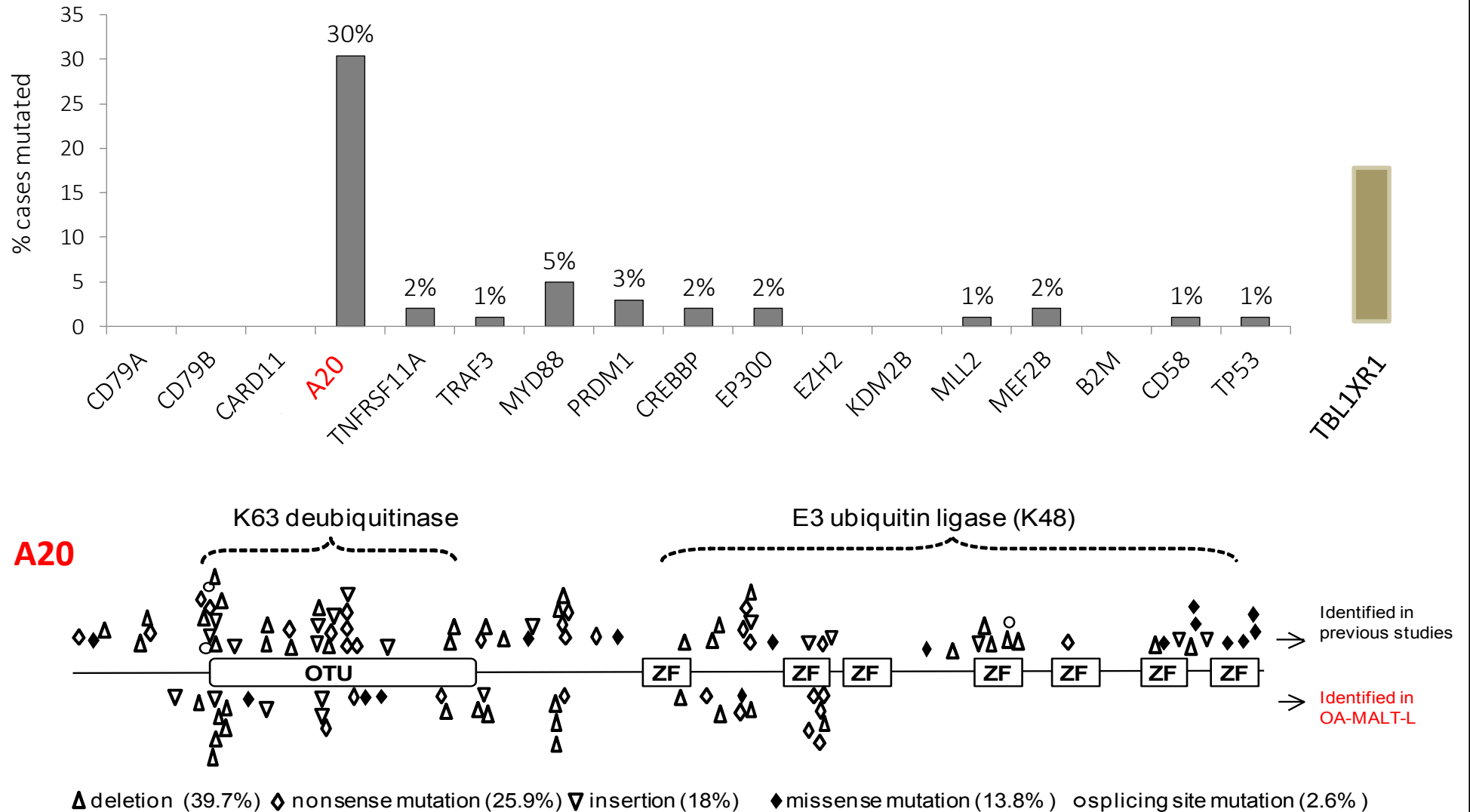
Du MQ, Semins Cancer Biol 2016
 Rosebeck et al Science 2011
 Nie et al Nat Commun 2015



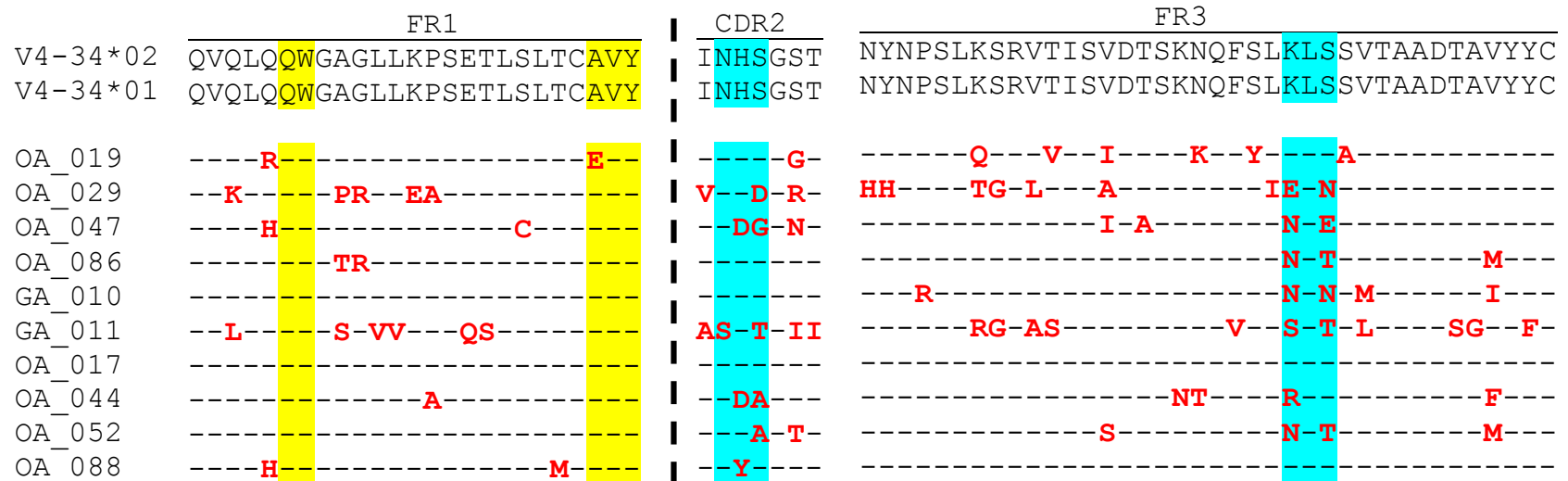
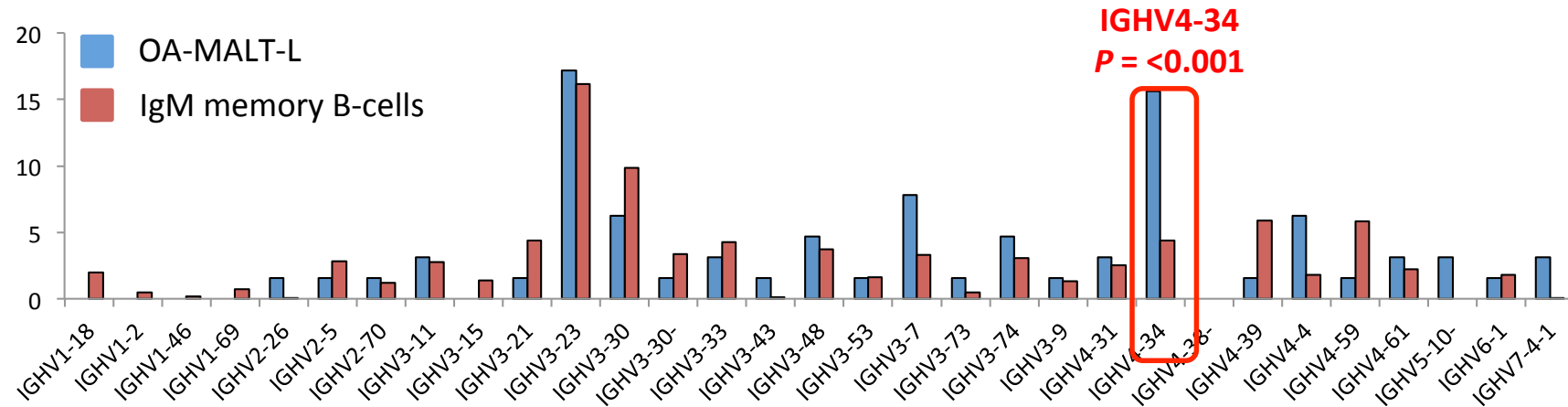
T(11;18): a marker for gastric MALT lymphoma not responding to *H. pylori* eradication

| | Complete remission | | | | No or partial remission | | | |
|--|--------------------|-----------|-----------------|------------|-------------------------|------------|--------------|------------|
| | No evidence of hRD | | Presence of hRD | | stage I | | ≥ stage II | |
| Europe | | | | | | | | |
| Apen et al Blood 2000 | 0/18 | 0% | | | | | | |
| Liu et al Gastroenterology 2002 | 0/46 | 0% | 2/2 | | 26/43 | 60% | 16/20 | 80% |
| Wundisch et al JCO 2005 | 3/46 | 7% | 4/7 | 57% | 3/13 | 23% | | |
| Montalban et al Ann Oncology 2005 | 0/11 | 0% | | | 0/2 | 0% | | |
| Levy, et al JCO 2005 | 0/21 | 0% | | | 1/7 | 14% | 2/3 | 67% |
| Ruskone-Fourmestraux, Du et al unpublished | 2/24 | 8% | 1/2 | 50% | 14/26 | 54% | 8/9 | 89% |
| Subtotal | 5/145 | 3% | 7/11 | 64% | 44/91 | 48% | 26/32 | 81% |
| Far East | | | | | | | | |
| Nakamura et al JCP 2003 | 0/11 | 0% | | | 0/4 | 0% | 0/4 | 0% |
| Iwano et al J Gastroenterology 2004 | 0/5 | 0% | | | 1/4 | 25% | 2/2 | 100% |
| Yeh et al Blood 2005 | 1/36 | 2.7 | | | 12/23 | 52% | | |
| Nakamura et al Gut 2007 | 1/20 | 5% | | | 5/14 | 36% | | |
| Nakamura et al AM J Gastr 2007 | 1/57 | 2% | | | 10/21 | 47% | 4/9 | 44% |
| Subtotal | 3/129 | 2% | | | 28/66 | 42% | 6/15 | 40% |
| Total | 8/274 | 3% | | | 71/150 | 47% | 30/44 | 68% |

MALT lymphoma lacks other mutations frequently seen in ABC-DLBCL



Biased usage of IG genes in OA-MALT lymphoma

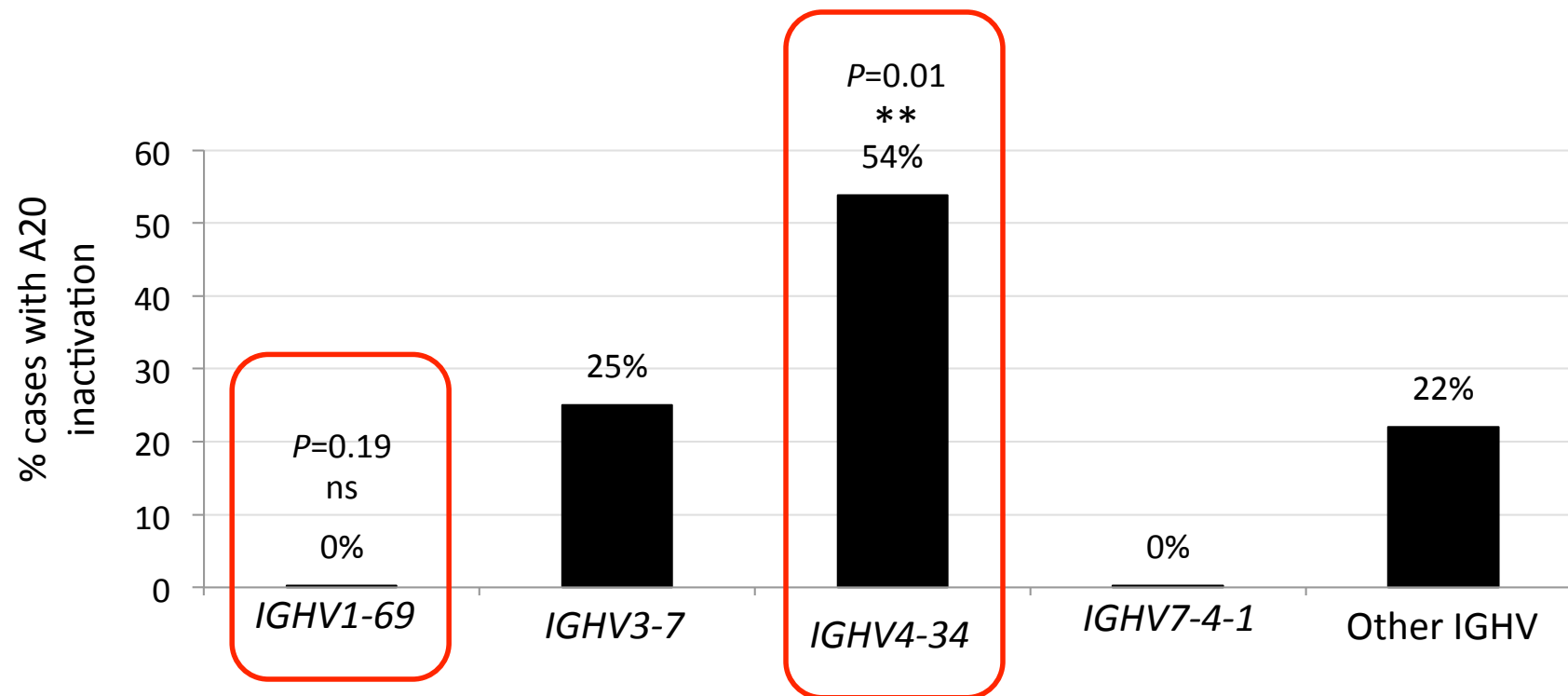


Maintain the QW/AVY
“hydrophobic patch” required for
binding to N-acetyl-lactosamine

Mutation hotspots:
N-glycosylation site (60%)
KLS motif (70%)

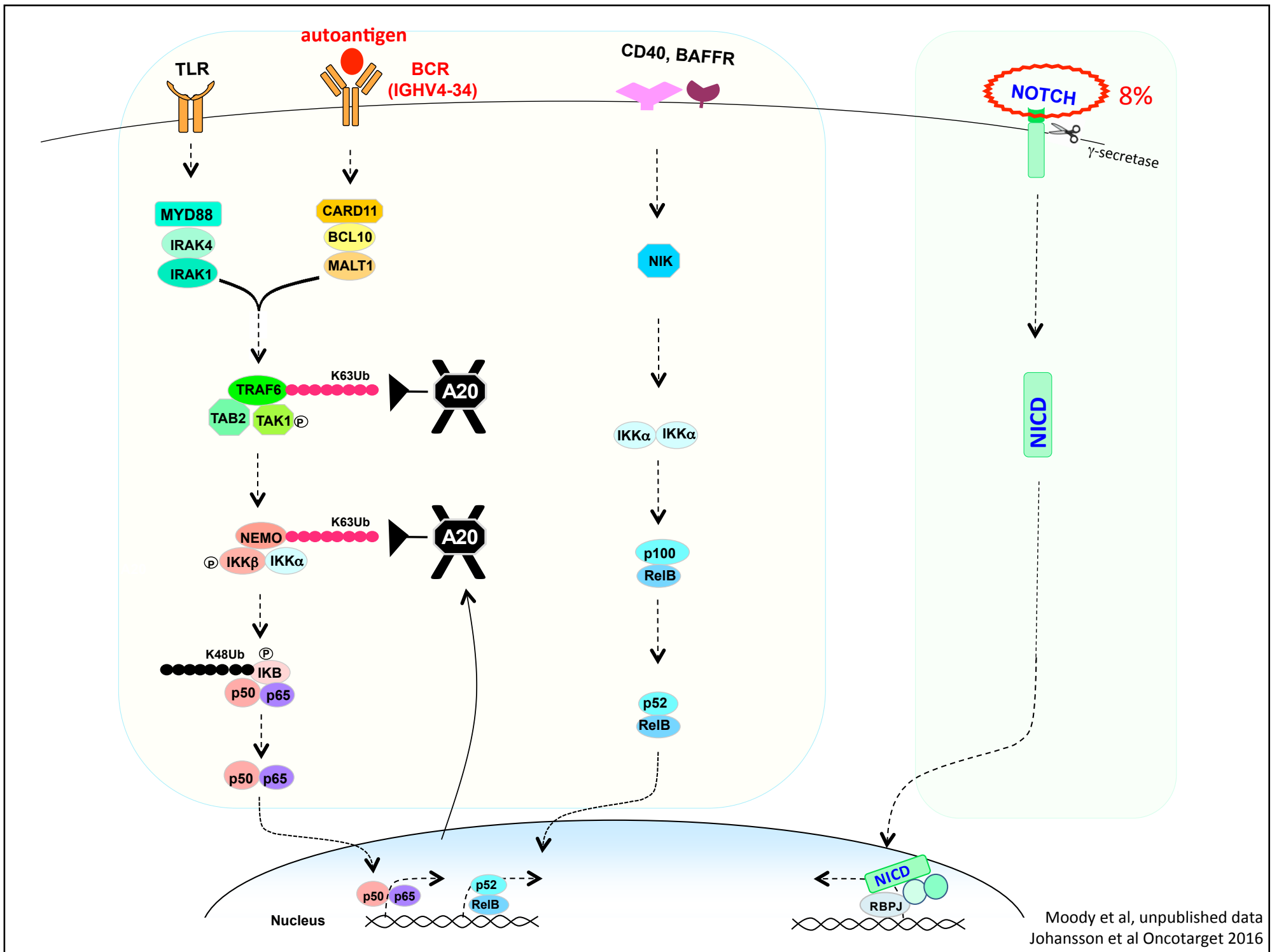
Zhu et al PlosOne 2011
Dagklis et al Leukaemia 2012
Zhu et al Leukaemia 2015
van Maldegenm et al Leukaemia 2012
Moody et al unpublished

Significant association between A20 mutation and IGHV4-34 usage in OA-MALT lymphoma



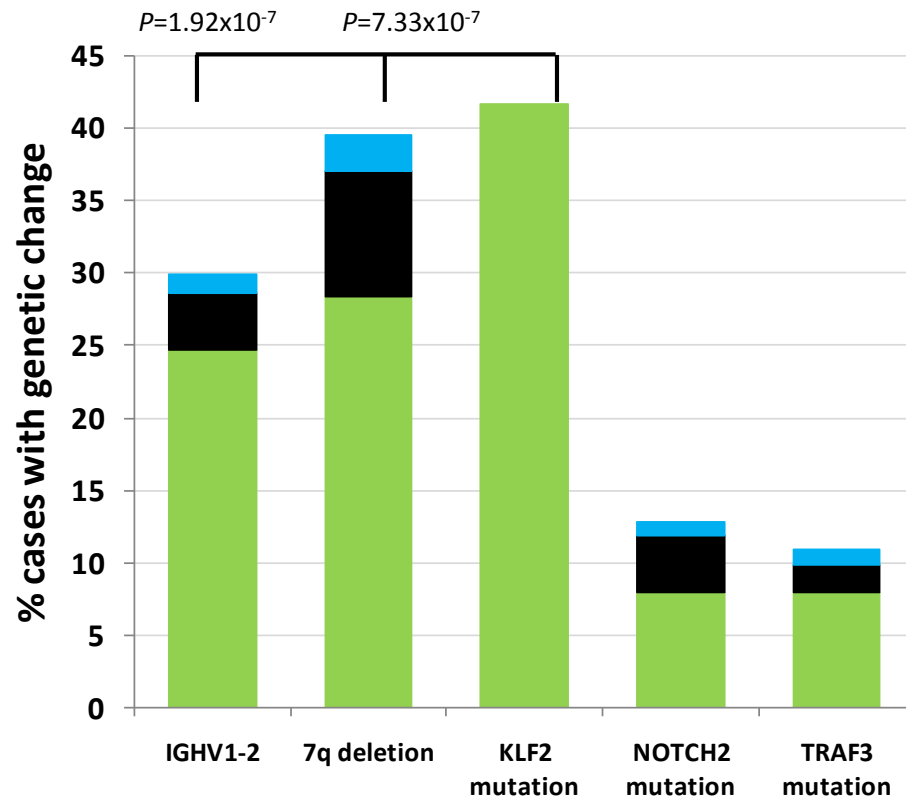
Salivary gland
MALT lymphoma

Ocular adnexal
MALT lymphoma



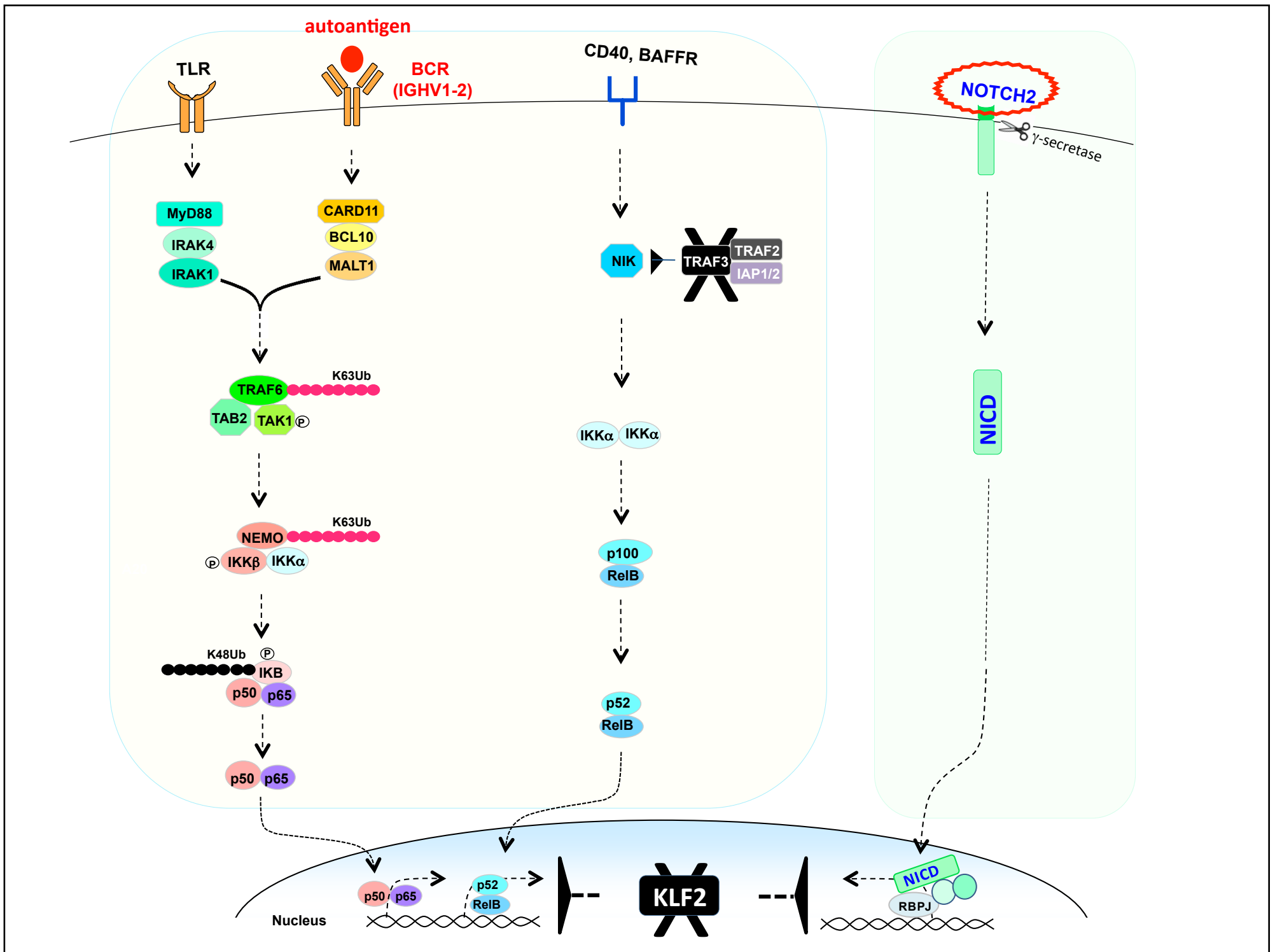
Moody et al, unpublished data
 Johansson et al Oncotarget 2016

KLF2 mutation and IGHV1-2 usage

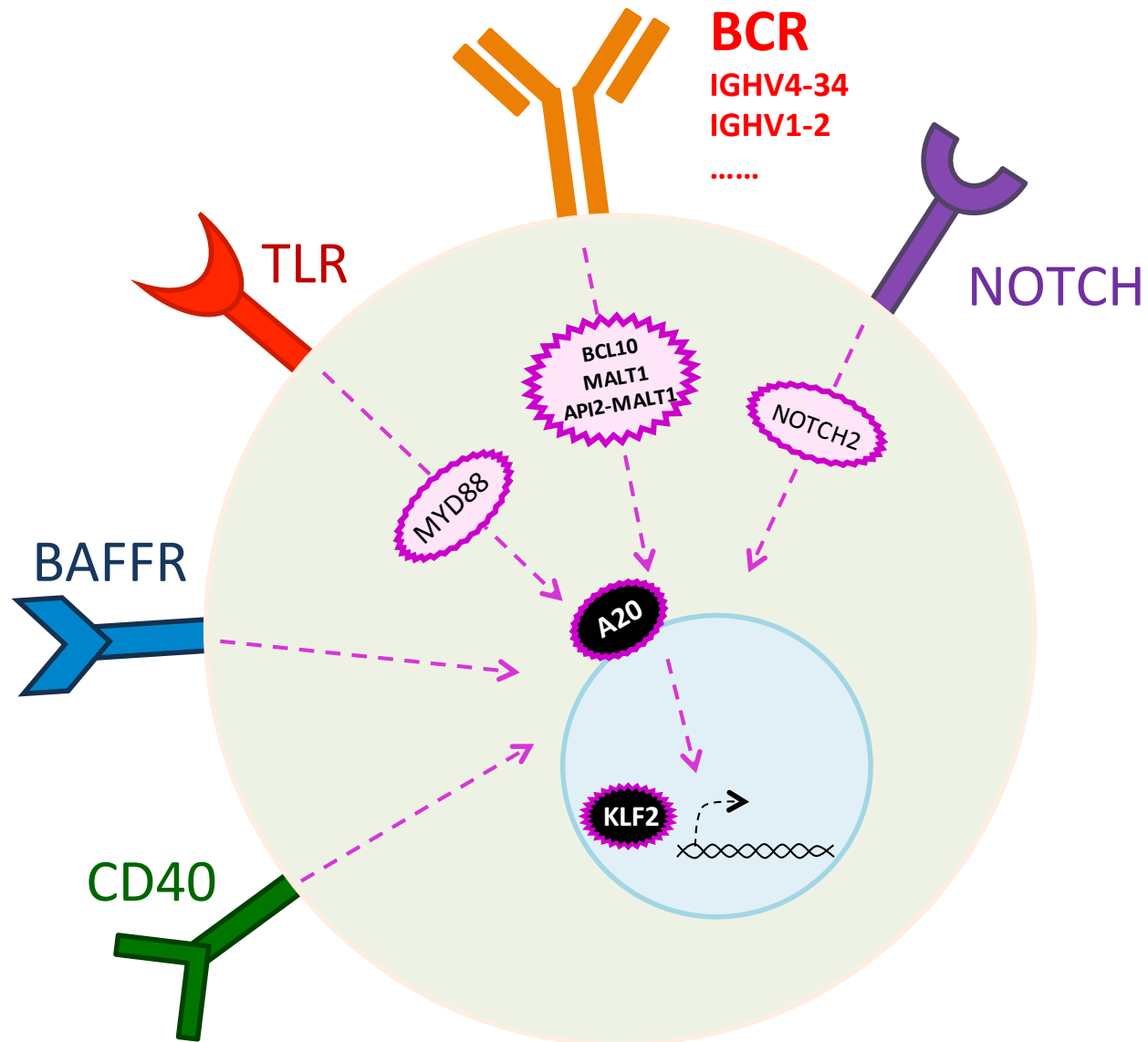


IGHV1-2 characteristics

- over-represented (~30%) in SMZL
- most being allele *04
- minimal somatic mutation
- long CDR3 with common motif
- often associated with biased use of light chain genes
- polyreactive to autoantigen by recombinant antibody studies



Marginal Zone lymphoma



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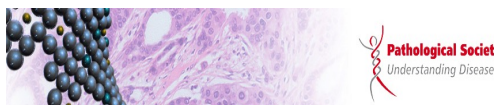
Laurence de Leval

Chi-Mei Medical Centre, Taiwan

Shih-Sung Chuang

Bloodwise

Beating blood cancer since 1960



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THE KAY KENDALL LEUKAEMIA FUND

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