In the name of

TargetTherapy of B cells in Renal Diseases

Hassan Argani; Professor of Nephrology

Immuno-pathogenesis of Glomerular disorders

Definition
&
Development of B cells

Target therapy for B cells

Immuno-pathogenesis of Glomerular disorders

Definition
&
Development of B cells

Target therapy for B cells

Major mechanisms by which immune events lead to capillary wall damage and proteinuria

Non-inflammatory pathways

Inflammatory pathways

Glomerular Ab Deposits

Sensitized T cells

Classical Complement Pathway

Lectin Pathway

Alternative Complement Pathway

C5b-9

C5a

GEC | GEN | MC

PMN/Platelets

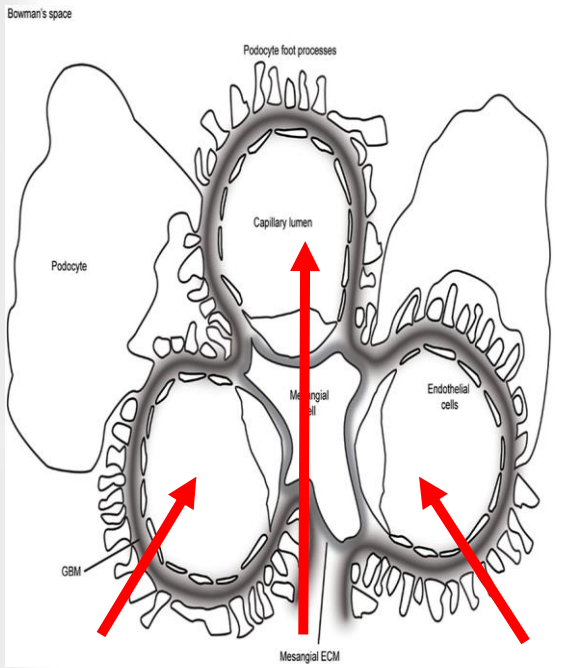
Macrophages

Oxidants, Proteases

Capillary wall damage, Proteinuria

Fibrin

Crescents



Intensity of inflammation

Table 1. Synoptic table summarizing pathogenetic mechanisms operating in both glomerular diseases (GN) and renal transplant damage

Pathogenetic mechanism	Glomerulonephritis	Kidney transplant damage
Complement activation	Lupus nephritis, post-infectious GN, cryoglobulinaemic GN, atypical haemolytic uraemic syndrome	AMR (CD4 perivascular deposits)
TLR ligation and DC activation	Lupus nephritis, IgA nephropathy	Alloimmune response in grafted kidneys
Circulating antibodies	Autoimmune GN, membranous GN	AMR
Transcription factors (NF-κB)	Nephrotic syndrome, IgA GN, lupus nephritis	AMR
Transcription factor JAK/STAT cytokine signalling	Experimental diabetes	Rejection injury
Renal fibrosis	GN progression	Failing transplant
Co-stimulatory molecules	Lupus nephritis	Renal graft rejection
B-cell activation	Lupus nephritis, vasculitis	AMR
Targeted therapy to one or more of the above mechanisms	Under study for application or already in use in glomerular diseases	Under study for application or already used in renal transplantation

Nephron Clin Pract 2011;119:c200–c204

Immuno-pathogenesis of Glomerular disorders

Definition & Development of B cells

Target therapy for B cells

Definition of Target therapy

Targeted therapy is a molecular modality for treatment of cancers or immunologic disorders.

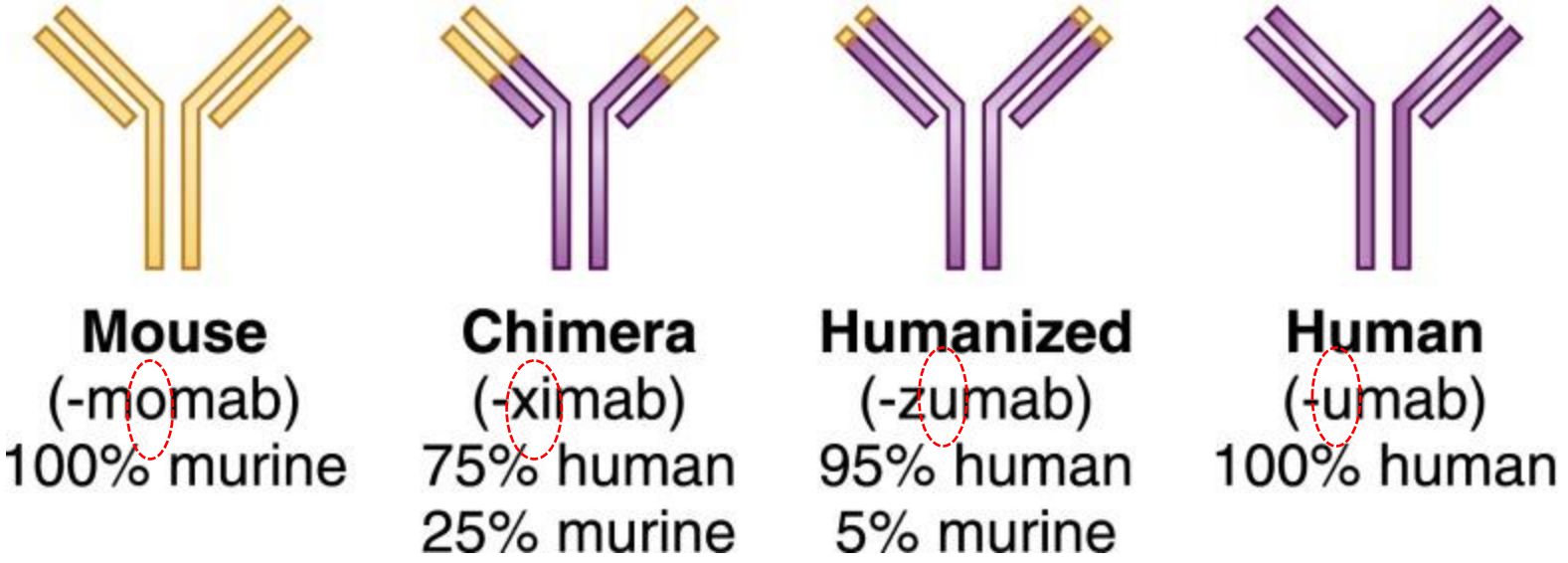

The Lowest Complication
The best dose of drug
The most Effective Drug

B cell directed therapies have proven for 2 types of Diseases:

1-Classic B cell/ autoantibody-driven disorders, such as autoimmune blistering skin diseases, myasthenia gravis, or antibody/immune-complex-mediated systemic lupus erythematosus (SLE).

2-Diseases that are believed to be **mainly driven by T cells**, most prominently rheumatoid arthritis (RA) or multiple sclerosis (MS)

The suffix denotes of the degree of human versus nonhuman components



Rituximab

ocrelizumab

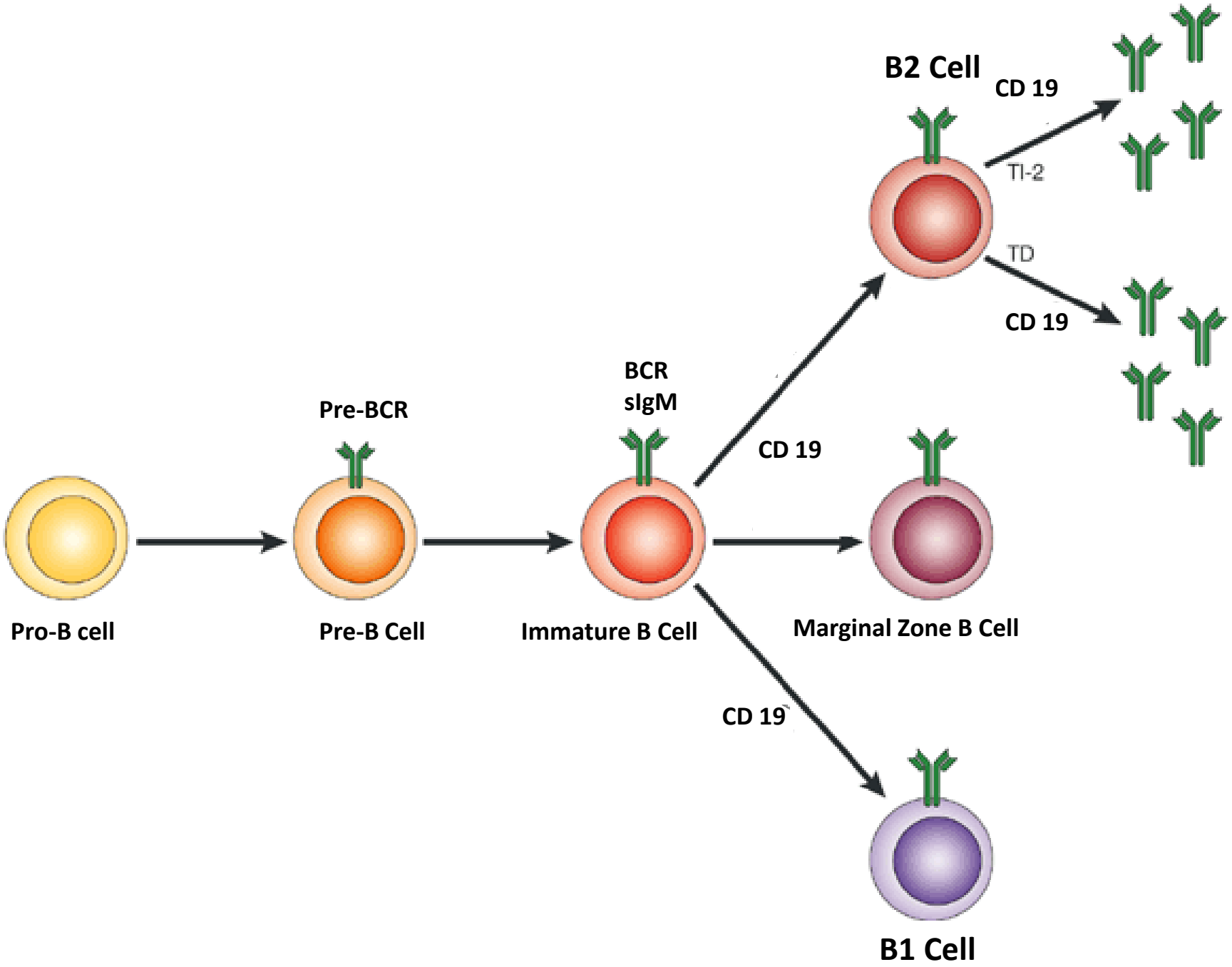
ofatumumab

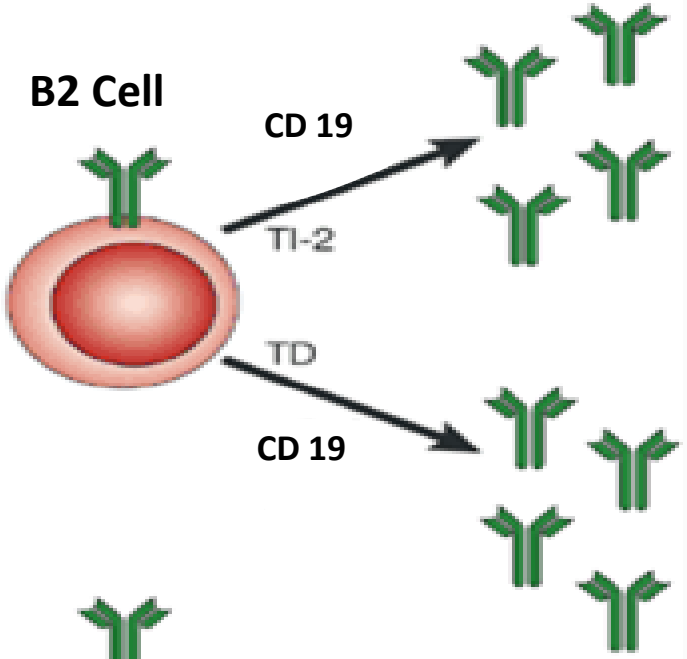
Drugs used by targeting B Cells

(I) Monoclonal antibodies against CD19, CD20, and CD22 that can directly target multiple B cell subtypes, but not or only to a lesser extent mature antibody-secreting plasma cells.

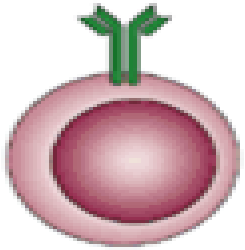
(II) Inhibitors of B cell activating factor (BAFF) and A proliferation-inducing ligand (APRIL), two cytokines which are very important survival factors for B cells and plasma cells, respectively.

III) velcade/bortezomib, a small molecule proteasome inhibitor that spares B cells but eliminates both short-lived and long-lived plasma cells


B2 Cell
CD 19
TI-2
TD
CD 19
BCR
sIgM
Pre-BCR
CD 19
Pro-B cell
Pre-B Cell
Immature B Cell
Marginal Zone B Cell
CD 19
B1 Cell

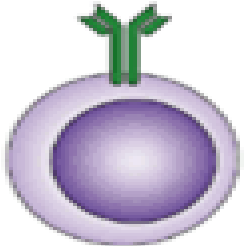


- Are activated in T-dependent immune responses.
- Produce antibodies of all subclasses.
- Are capable of forming memory B cells with increased antibody affinity
- Produces the majority of Bregs.



Marginal Zone B Cell

- Are found in the marginal sinus of the white pulp of the spleen.
- Predominantly produce antibodies that are specific for carbohydrate antigens



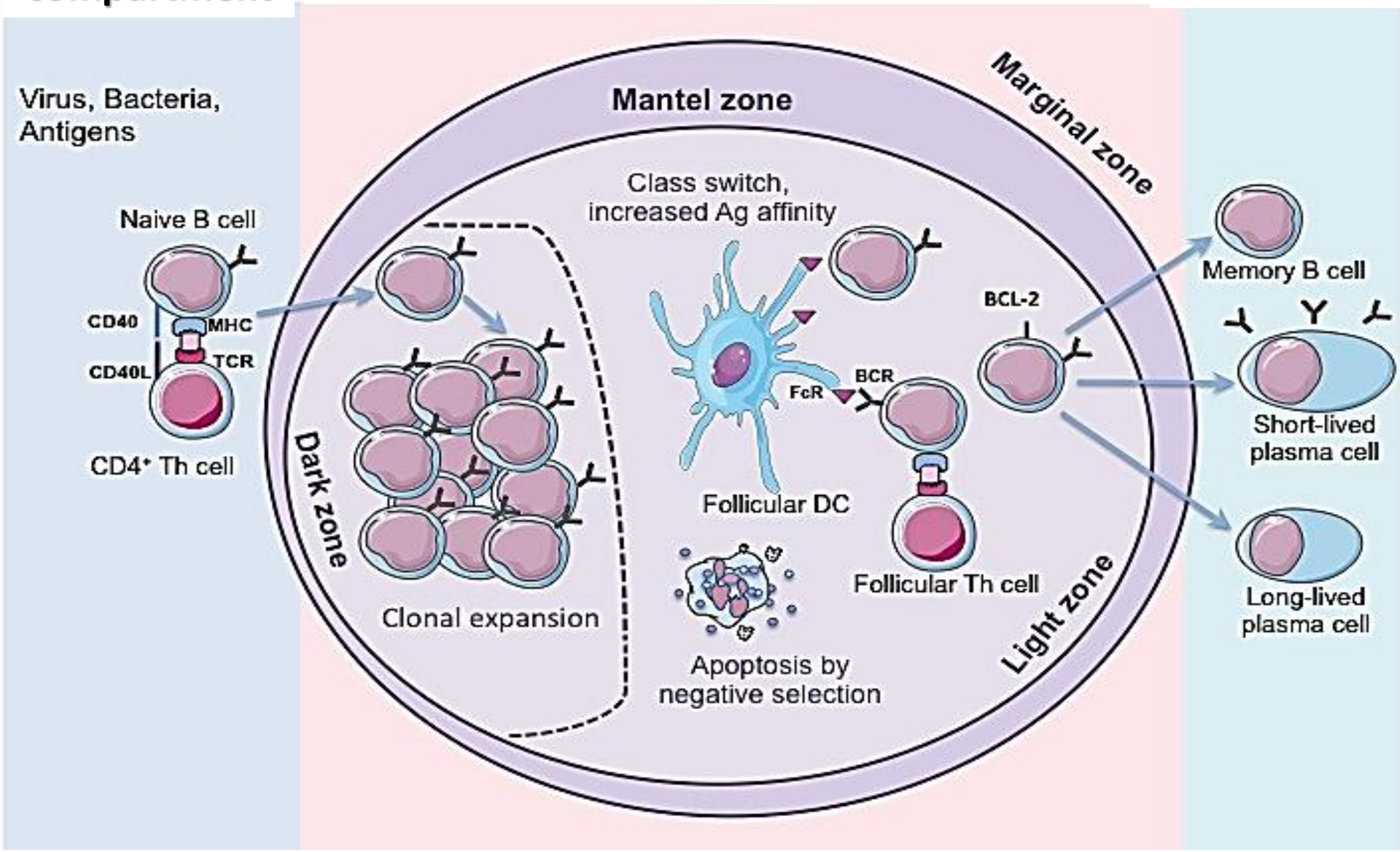
B1 Cell

- Arise early in embryonic development.
- Comprised about 5% of all B cells.
- Is the major source of **natural IgM antibodies** that exhibit reactivity to self and common microbial antigens.
- acts as a first line of defense against pathogens.

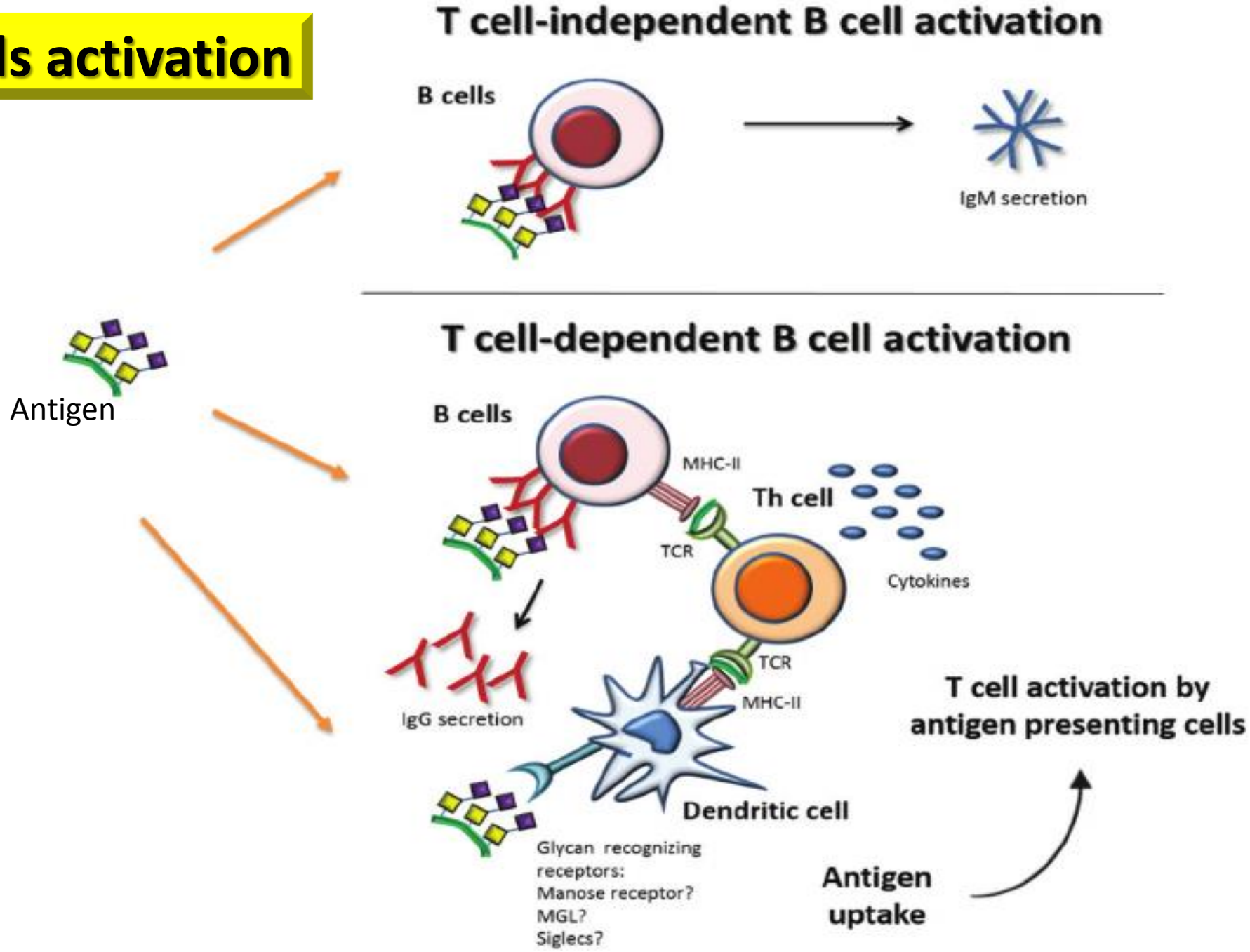
Peripheral compartment

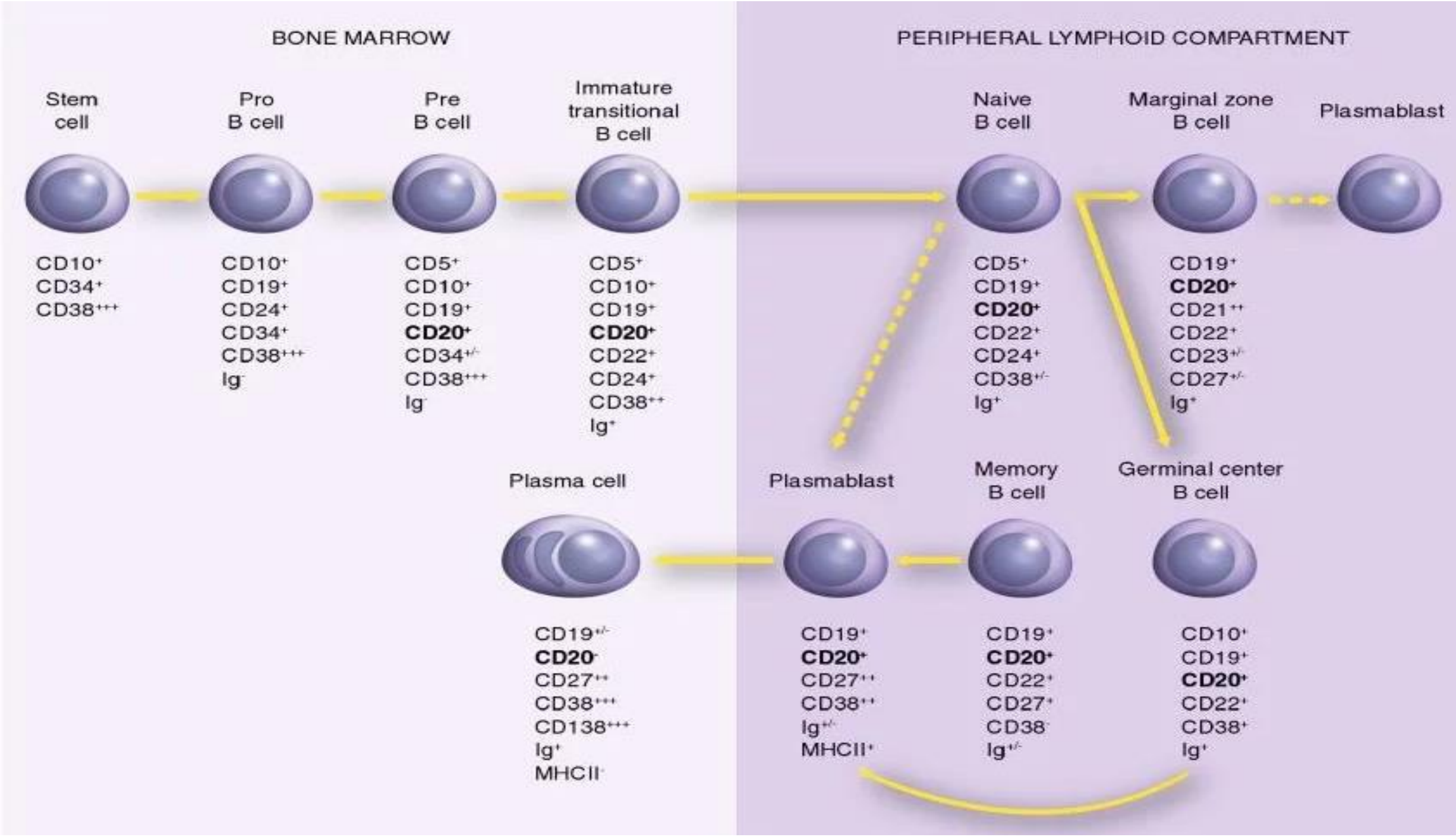
Spleen, Lymph node

Inflamed Tissue, Bone marrow

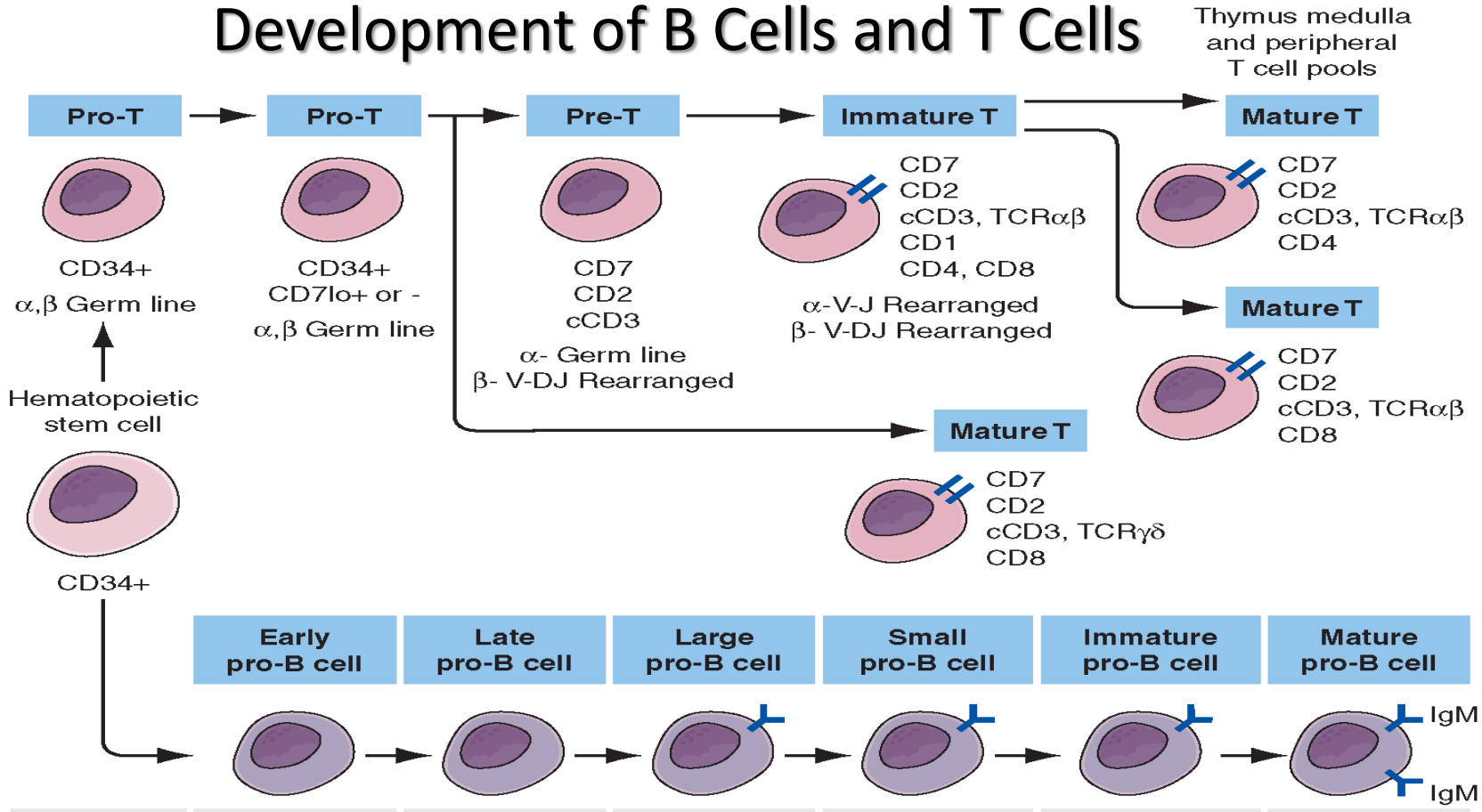


Types of B cells activation



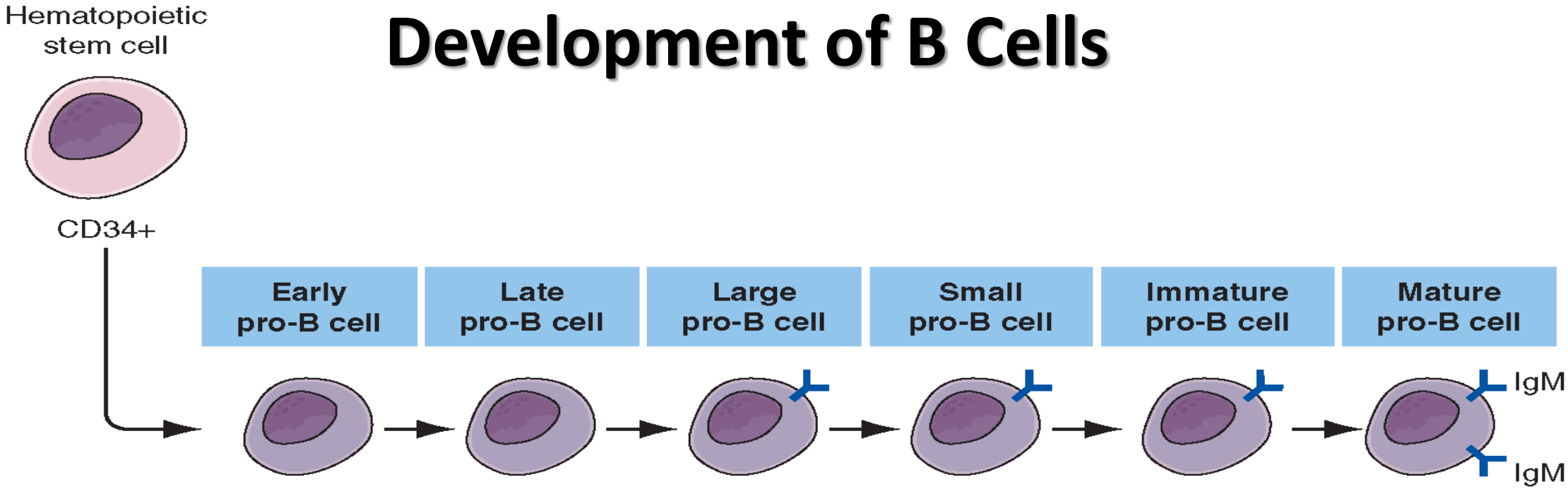

BONE MARROW
PERIPHERAL LYMPHOID COMPARTMENT
Stem cell
CD10+
CD34+
CD38+++
Pro B cell
CD10+
CD19+
CD24+
CD34+
CD38+++
Ig-
Pre B cell
CD5+
CD10+
CD19+
CD20+
CD34+/-
CD38+++
Ig-
Immature transitional B cell
CD5+
CD10+
CD19+
CD20+
CD22+
CD24+
CD38++
Ig+
Naive B cell
CD5+
CD19+
CD20+
CD22+
CD24+
CD38+/-
Ig+
Marginal zone B cell
CD19+
CD20+
CD21++
CD22+
CD23+/-
CD27+/-
Ig+
Plasmablast
Plasma cell
CD19+/-
CD20-
CD27++
CD38+++
CD138+++
Ig+
MHCII-
Plasmablast
CD19+
CD20+
CD27++
CD38++
Ig+/-
MHCII+
Memory B cell
CD19+
CD20+
CD22+
CD27+
CD38-
Ig+/-
Germinal center B cell
CD10+
CD19+
CD20+
CD22+
CD38+
Ig+

Development of B Cells and T Cells



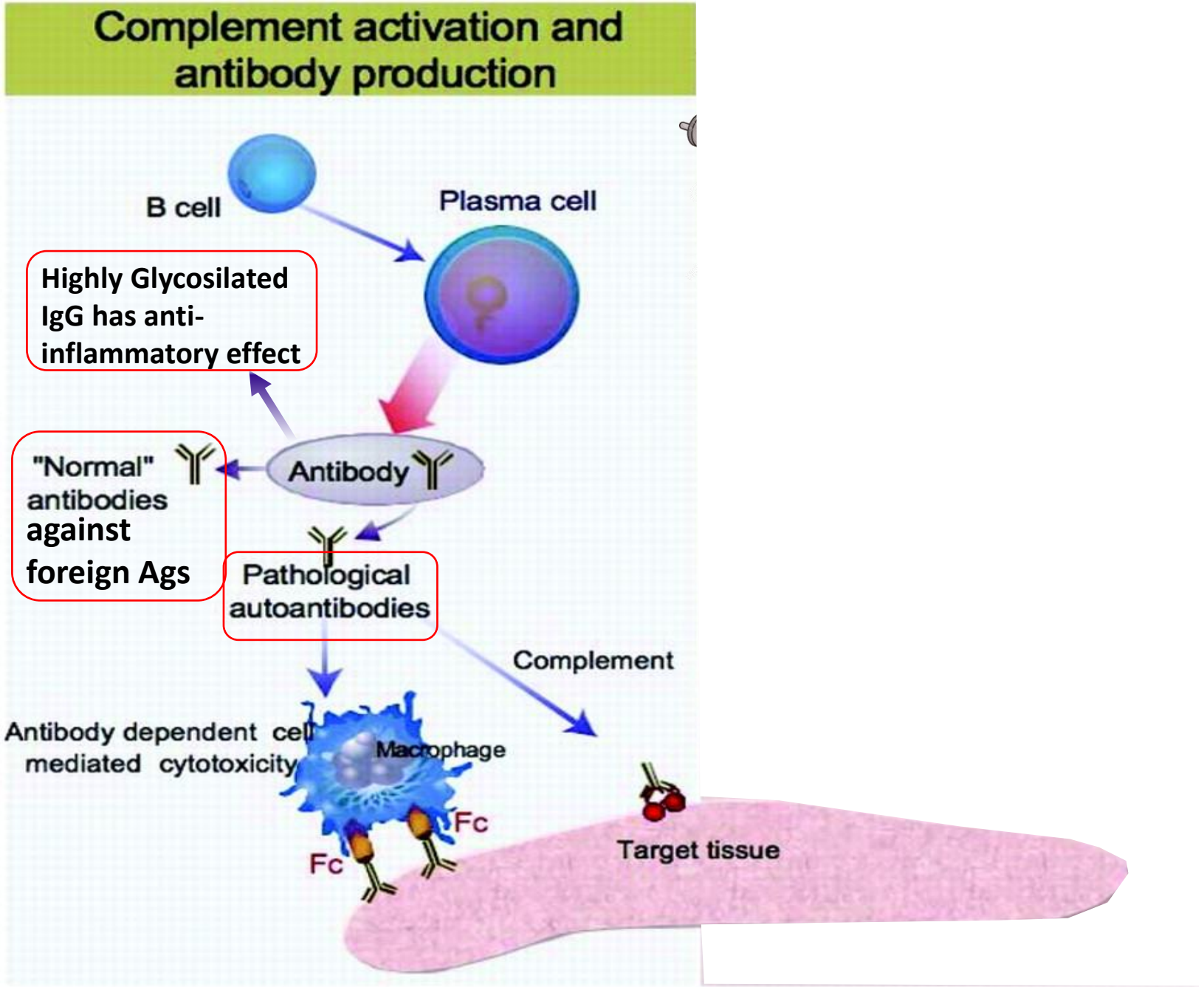
High-chain genes	DJ rearranged	VDJ rearranged	VDJ rearranged	VDJ rearranged	VDJ rearranged	VDJ rearranged
Low-chain genes	Germ line	Germ line	Germ line	VDJ rearranged	VDJ rearranged	VDJ rearranged
Surface Ig	Absent	Absent	μ H-chain at surface as part of pre-β receptor	μ H-chain in cytoplasm and at surface	IgM expressed on cell surface	IgD and IgM made from alternatively spliced H-chain transcripts
Surface marker proteins	CD34 CD10 CD19 CD38	CD10 CD19 CD20 CD38 CD40	CD19 CD20 CD38 CD40	CD19 CD20 CD38 CD40	CD19 CD20 CD40	CD19 CD20 CD21 CD40

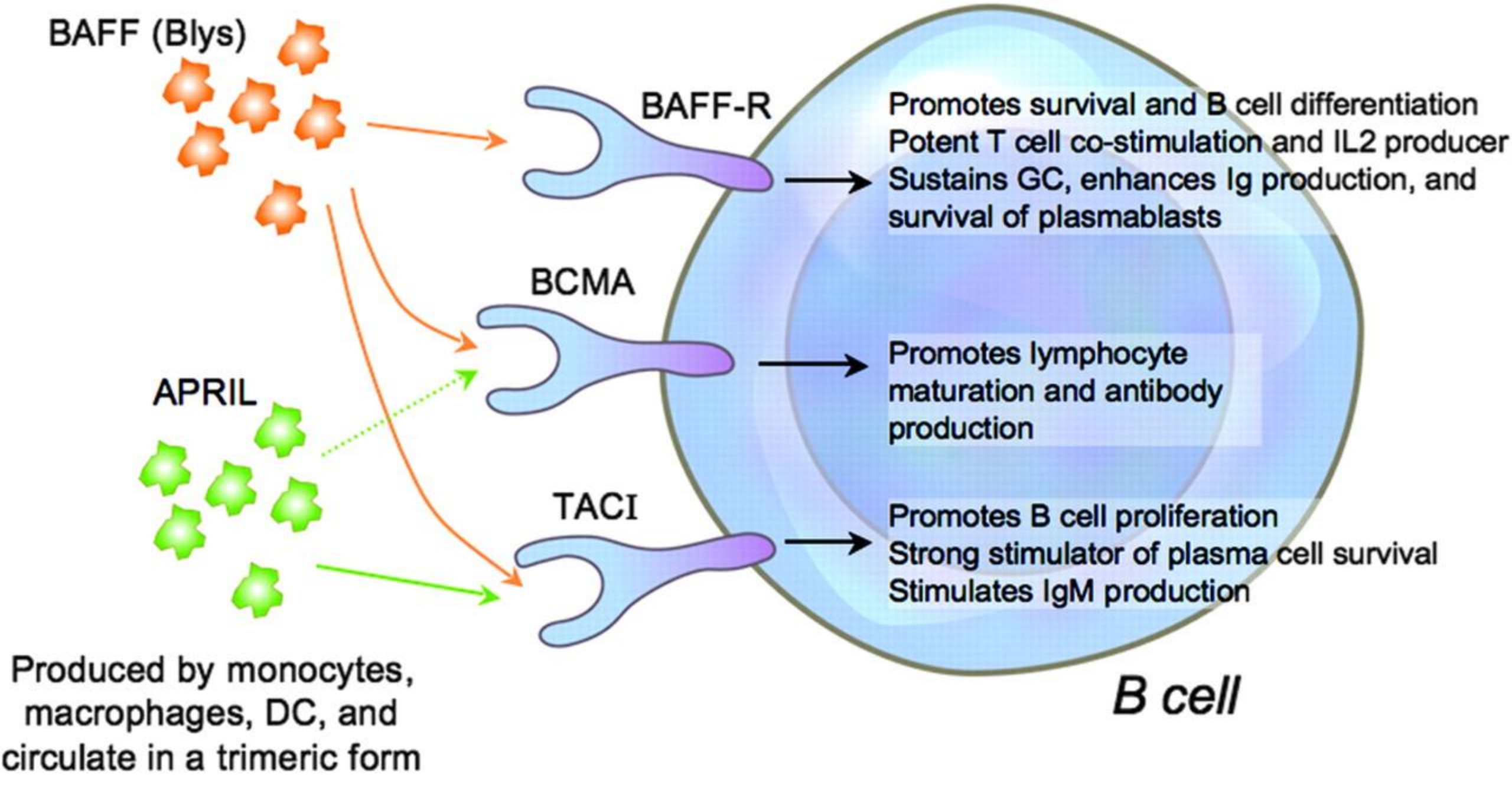
Development of B Cells



	Early pro-B cell	Late pro-B cell	Large pro-B cell	Small pro-B cell	Immature pro-B cell	Mature pro-B cell
High-chain genes	DJ rearranged	VDJ rearranged	VDJ rearranged	VDJ rearranged	VDJ rearranged	VDJ rearranged
Low-chain genes	Germ line	Germ line	Germ line	VDJ rearranged	VDJ rearranged	VDJ rearranged
Surface Ig	Absent	Absent	μ H-chain at surface as part of pre-β receptor	μ H-chain in cytoplasm and at surface	IgM expressed on cell surface	IgD and IgM made from alternatively spliced H-chain transcripts
Surface marker proteins	CD34 CD10 CD19 CD38	CD10 CD19 CD20 CD38 CD40	CD19 CD20 CD38 CD40	CD19 CD20 CD38 CD40	CD19 CD20 CD40	CD19 CD20 CD21 CD40

B cell functions




BAFF (Blys)
APRIL
BAFF-R
BCMA
TACI
Promotes survival and B cell differentiation
Potent T cell co-stimulation and IL2 producer
Sustains GC, enhances Ig production, and survival of plasmablasts
Promotes lymphocyte maturation and antibody production
Promotes B cell proliferation
Strong stimulator of plasma cell survival
Stimulates IgM production
B cell
Produced by monocytes, macrophages, DC, and circulate in a trimeric form

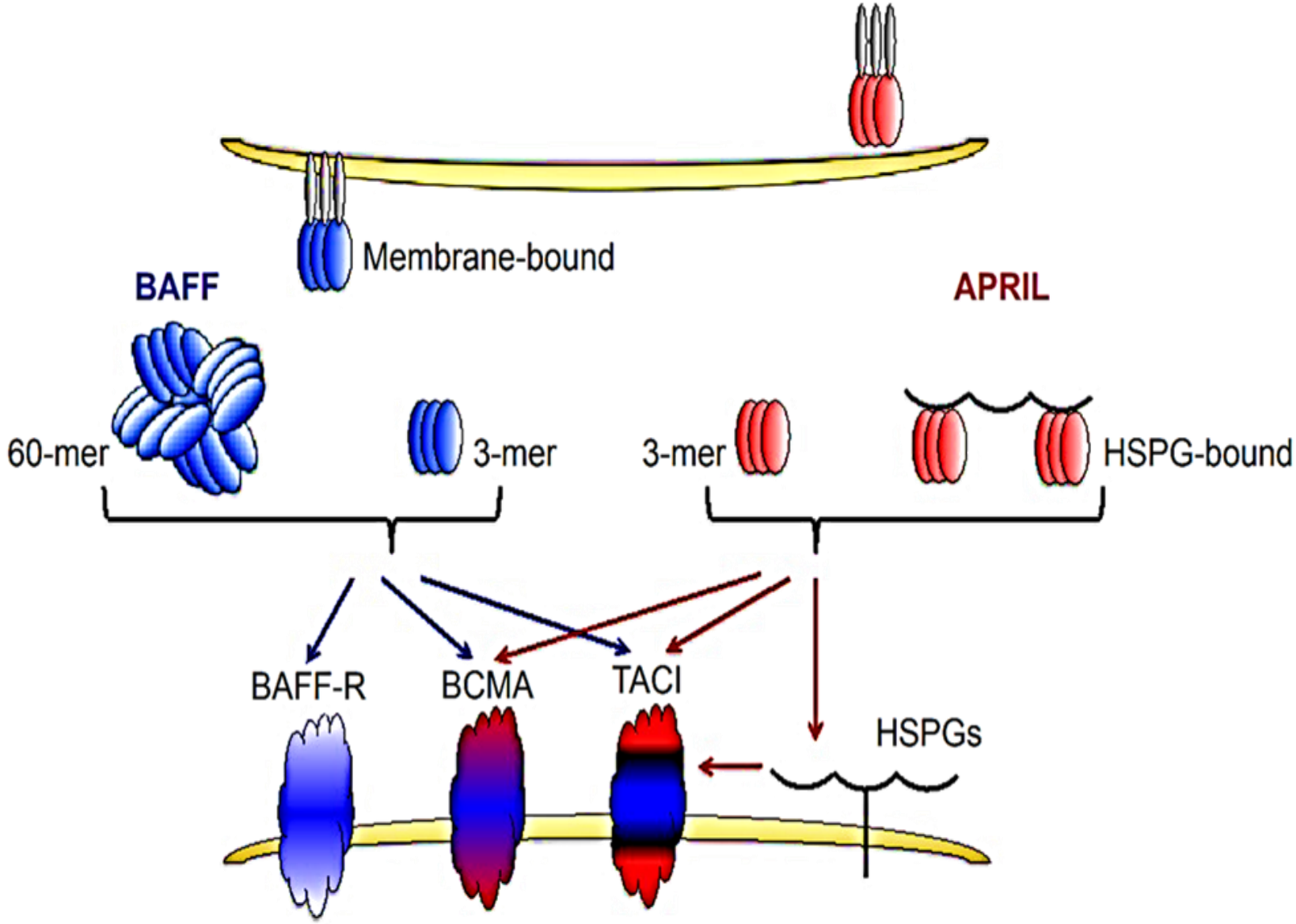


Figure 1 Interaction between BAFF and APRIL and their receptors.

Abbreviations: APRIL, a proliferation-inducing ligand; BAFF, B cell activating factor of the TNF family; BCMA, B-cell maturation antigen; HSPGs, heparin-sulfate proteoglycans; TACI, transmembrane activator and calcium modulator and cyclophilin ligand interactor.

Drug Design, Develop.Therapy;2017:11 Pages 747—757

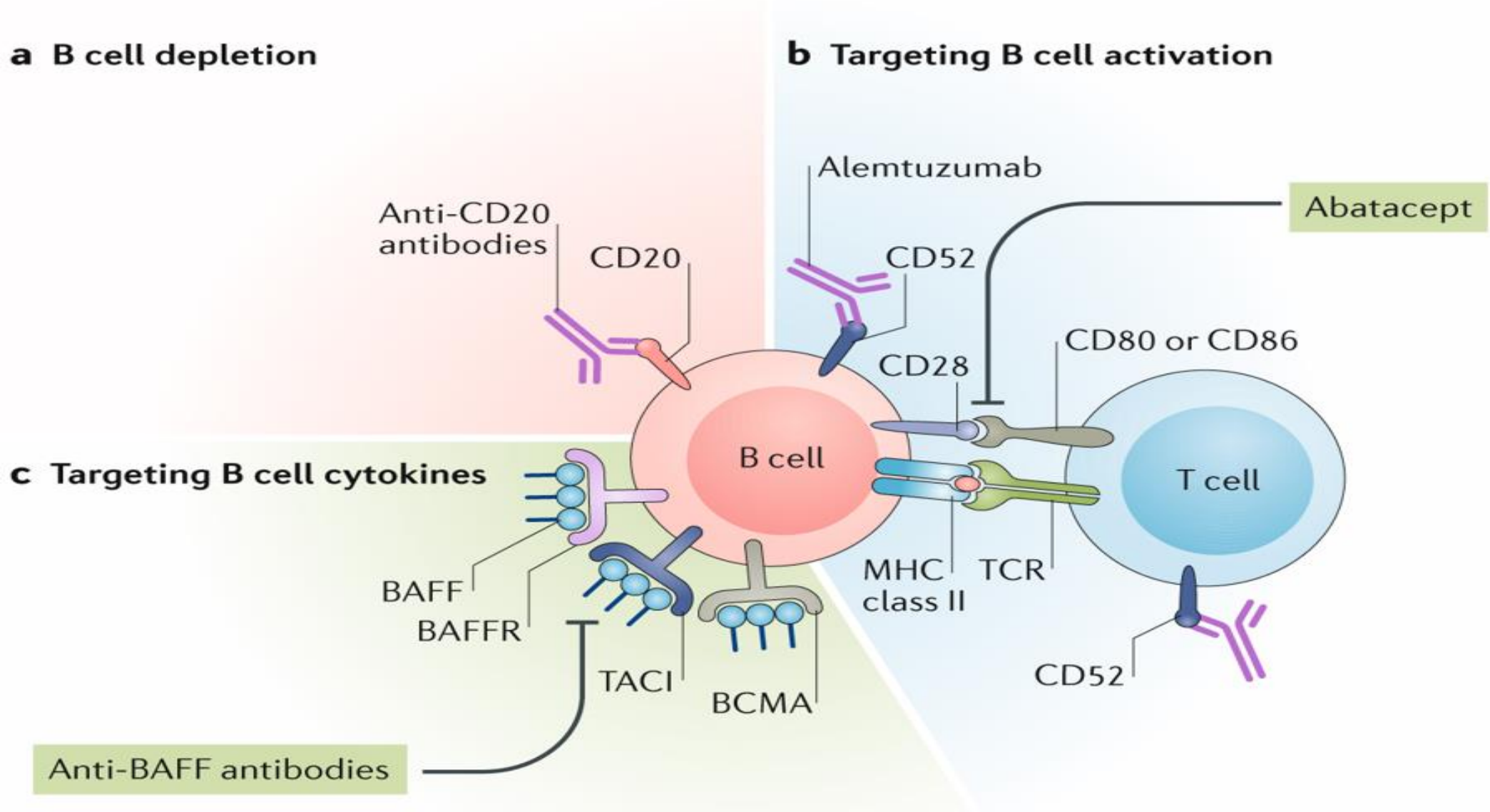
Definition
&
Development of B cells

Immuno-pathogenesis of Glomerular disorders

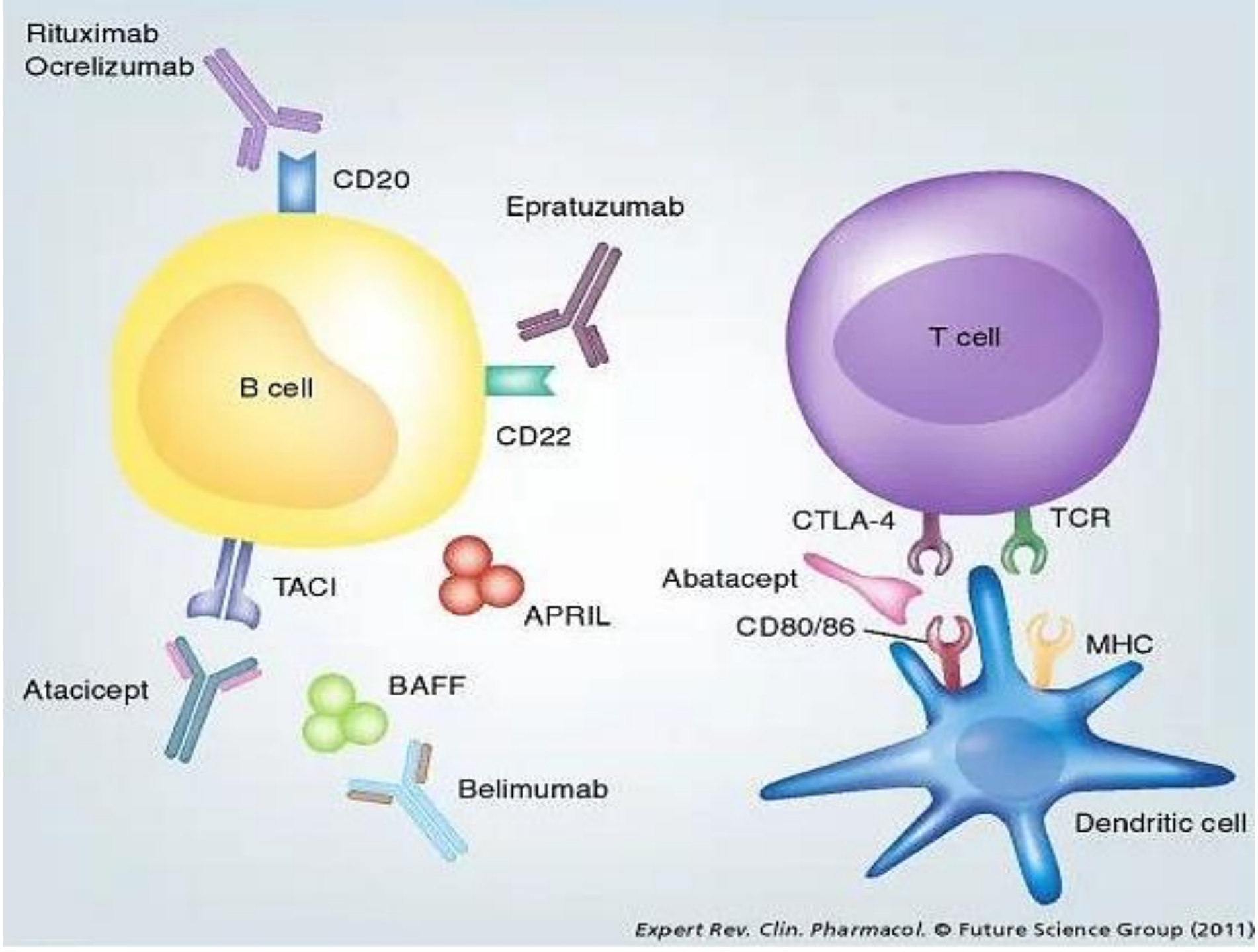
Target therapy for B cells

Methods of therapeutically targeting B cells

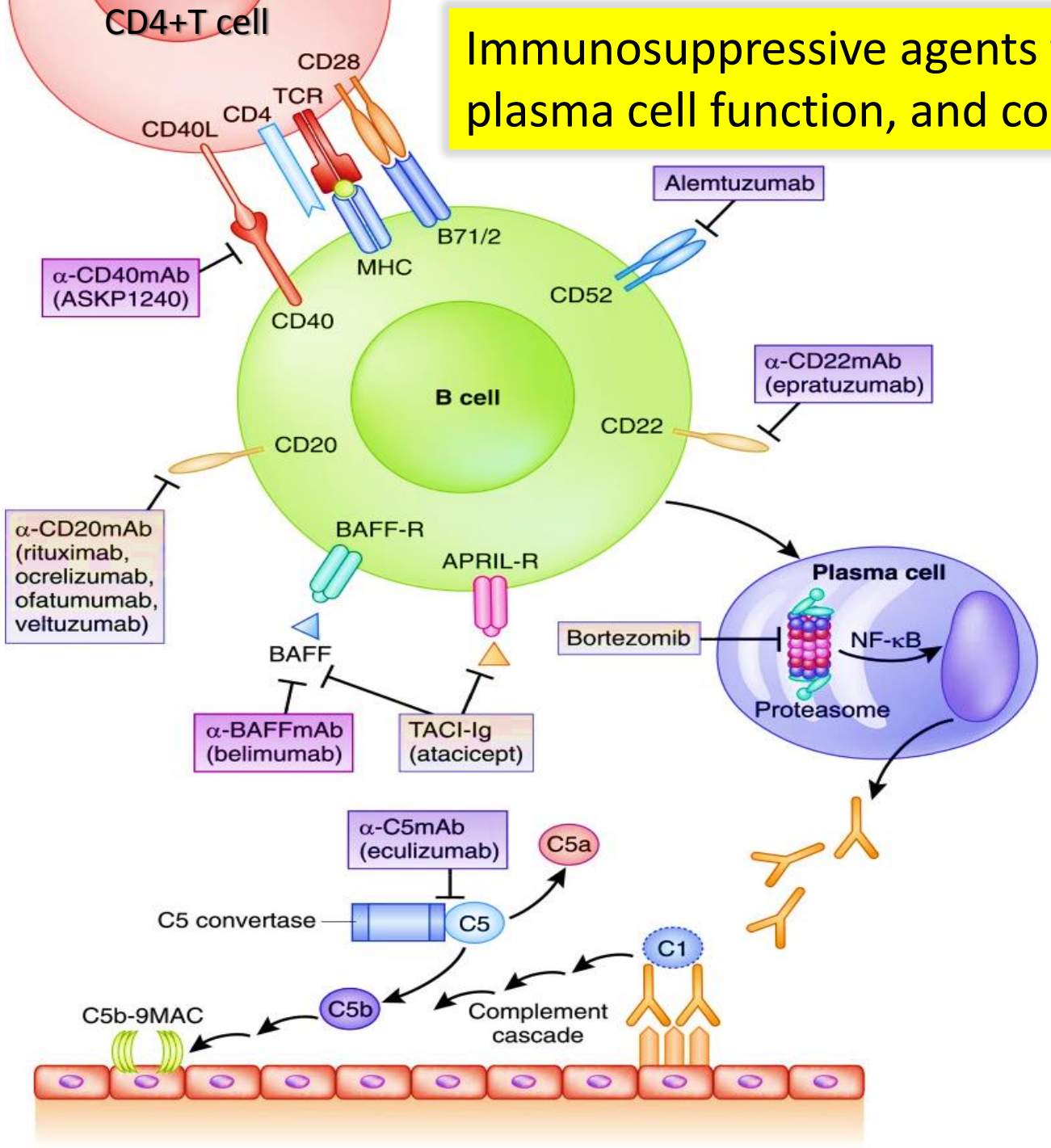
Methods of therapeutically targeting B cells



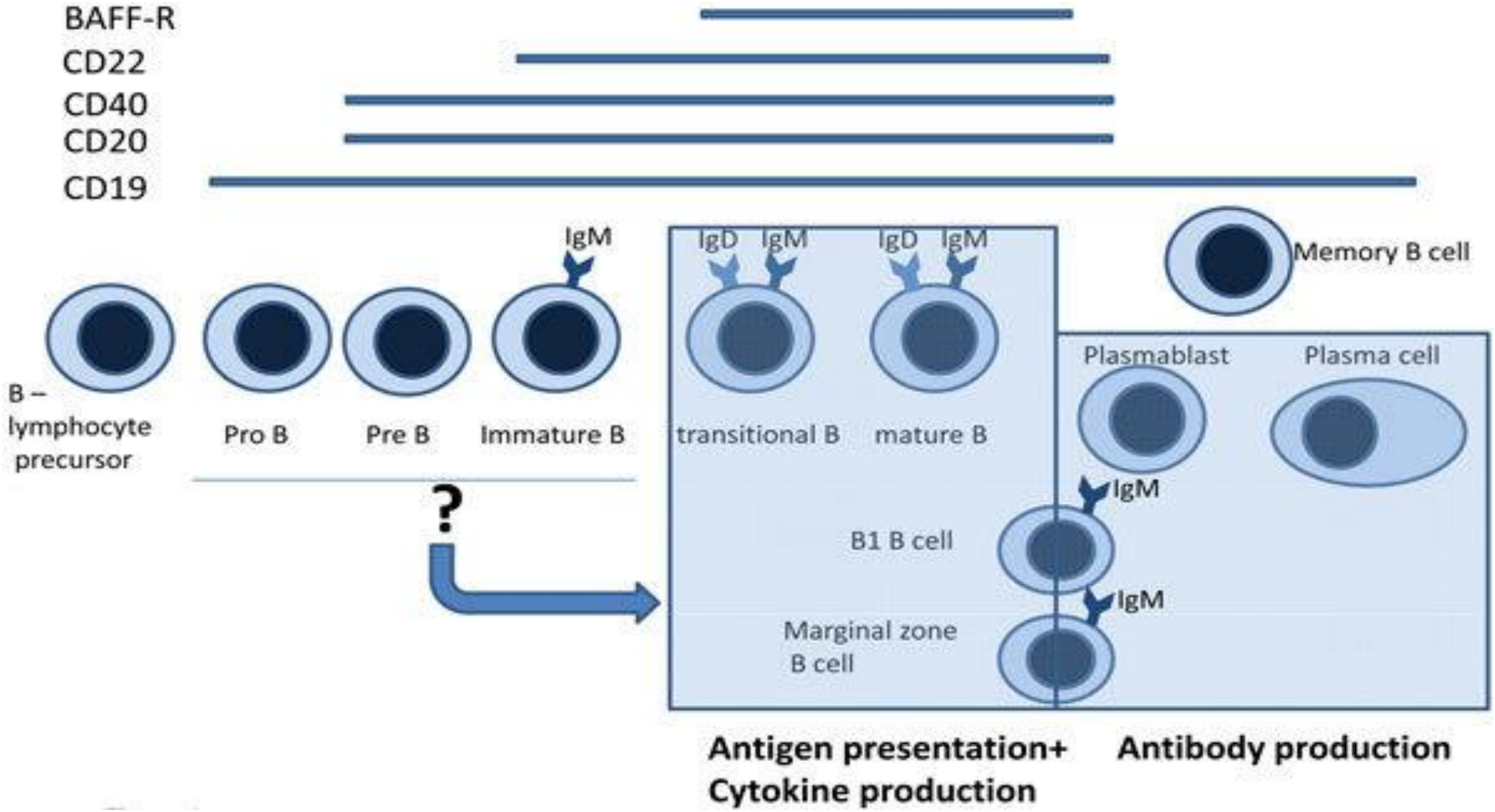
Nature Reviews Rheumatologyvolume 14, pages580–591 (2018)


Rituximab
Ocrelizumab
CD20
Epratuzumab
B cell
CD22
T cell
CTLA-4
TCR
Abatacept
CD80/86
MHC
TACI
APRIL
Atacicept
BAFF
Belimumab
Dendritic cell
Expert Rev. Clin. Pharmacol. © Future Science Group (2011)

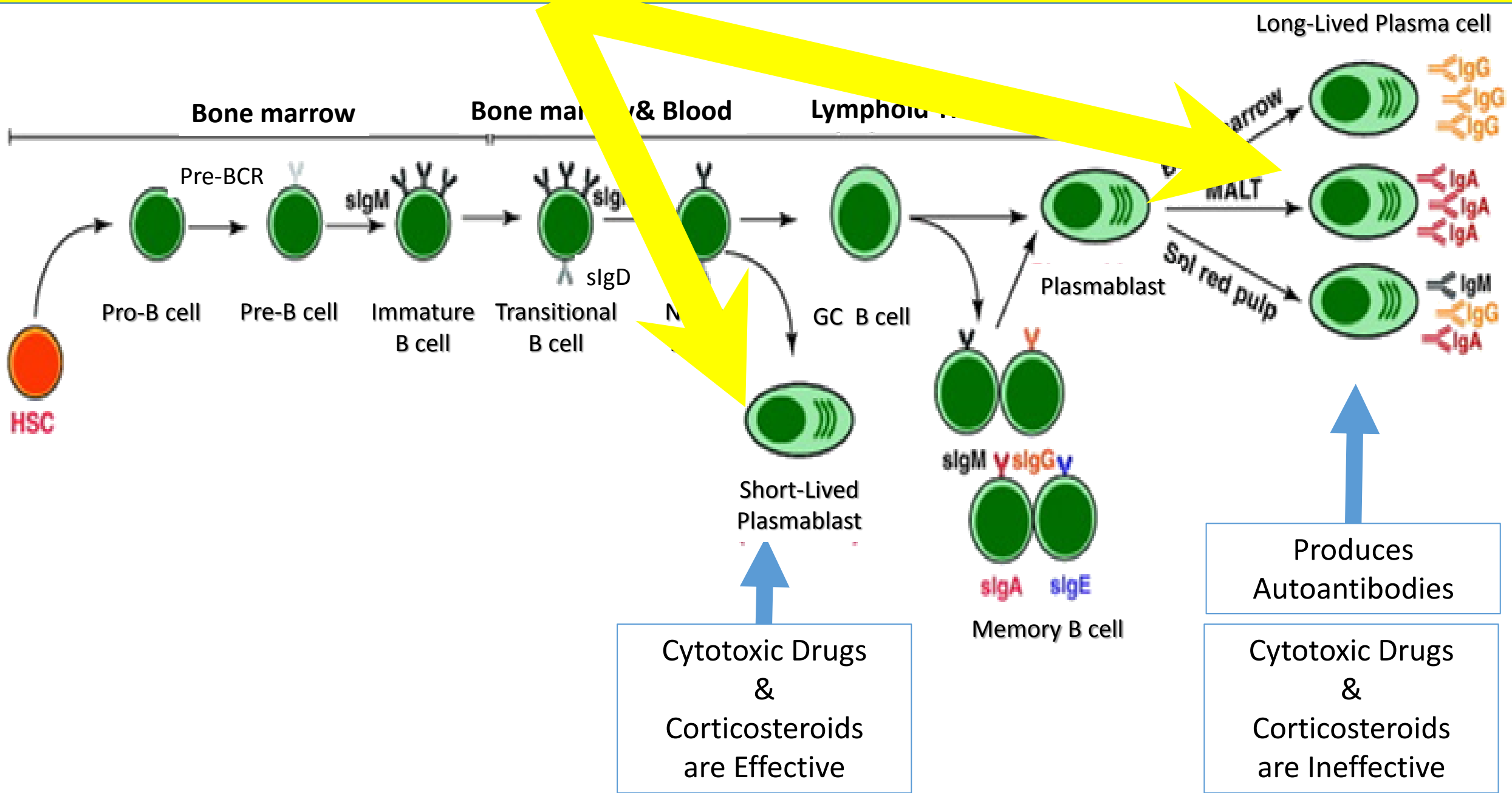
Immunosuppressive agents targeting T cell/B cell interaction, plasma cell function, and complement-mediated injury.



Schematic representation of B-cell differentiation and maturation states.



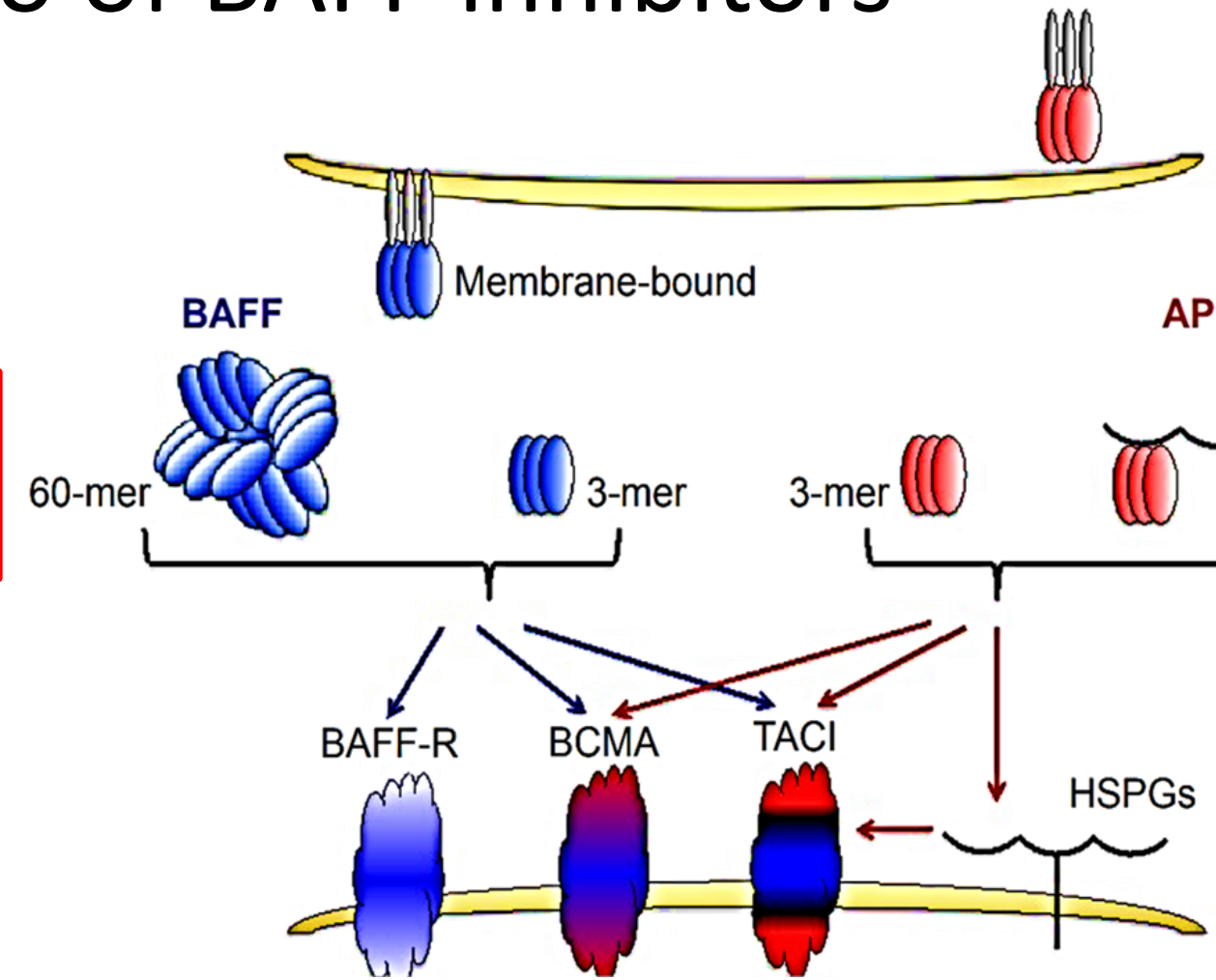
Bortezomib efficiently depletes both short-lived and long-lived plasma cells



The portfolio of BAFF inhibitors

Belimumab (anti-BAFF antibody)
Blisibimod (anti-BAFF peptibody)
Tabalumab (anti-BAFF antibody)

Briobacept (BAFF receptor Ab)



Atacicept (TACI receptor, inhibits both BAFF and APRIL)

Drug Design, Development and Therapy;2017:11 Pages 747—757

NEPHROLOGY

Original Article

B-cell activating factor, a predictor of antibody mediated rejection in kidney transplantation recipients

Wannarat Pongpirul, Wiwat Chancharoenthana, Krit Pongpirul, Asada Leelahavanichkul, Wipawee Kittikowit, Kamonwan Jutivorakool, Bunthoon Nonthasoot, Yingyos Avihingsanon, Somchai Eiam-Ong, Kearkiat Praditpornsilpa, Natavudh Townamchai

Aim

Donor-specific antibody (DSA) is a widely-used biomarker for antibody-mediated rejection (ABMR) but correctly indicates only 30–40% of patients with ABMR. Additional biomarkers of ABMR in kidney transplant recipients are needed.

Nephrology (Carlton). 2018 Feb;23(2):169-174

Conclusion

Post-transplant ABMR can be predicted by perioperative serum BAFF level. Together with DSA testing, BAFF provides additional predictive value for ABMR.

Nephrology (Carlton). 2018 Feb;23(2):169-174

American Journal of Transplantation 2016; 16: 1266–1275
Wiley Periodicals Inc.

doi: 10.1111/ajt.13557

Effect of Treatment With Tabalumab, a B Cell–Activating Factor Inhibitor, on Highly Sensitized Patients With End-Stage Renal Disease Awaiting Transplantation

M. A. Mujtaba[1,*], W. J. Komocsar[2], E. Nantz[2], M. D. Samaniego[3], S. L. Henson[4], J. A. Hague[5], A. L. Lobashevsky[6], N. G. Higgins[6], M. Czader[7], B. K. Book[4], M. D. Anderson[8], M. D. Pescovitz[†] and T. E. Taber[8]

[1]*Division of Nephrology, University of Texas Medical Branch, Galveston, TX*
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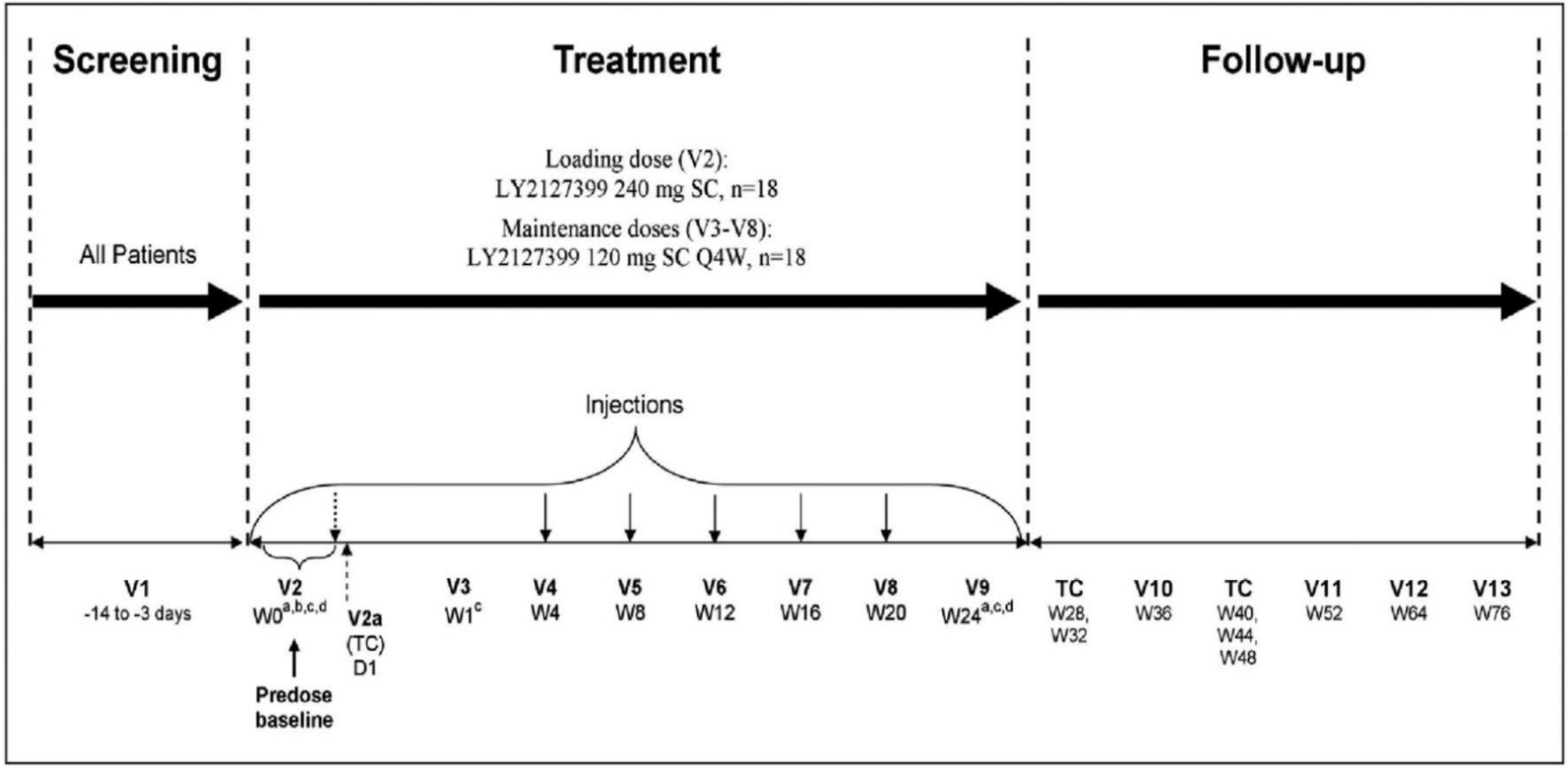
[3]*Department of Internal Medicine—Nephrology, University of Michigan Health System, Ann Arbor, MI*
[4]*Department of Surgery, Indiana University School of Medicine, Indianapolis, IN*
[5]*Clinical Trial Management, Eli Lilly and Company, Indianapolis, IN*
[6]*Transplant Immunology, Indiana University Health, Indianapolis, IN*
[7]*Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, IN*
[8]*Department of Medicine—Nephrology, Indiana*

tabalumab-related serious adverse events occurred (pneumonia, worsening of peripheral neuropathy), while the most common other adverse events were injection-site pain and hypotension. Three patients received matched deceased donor transplants during follow-up. Treatment with a BAFF inhibitor resulted in statistically significant, but not clinically meaningful reduction in the cPRA from baseline (NCT01200290, Clinicaltrials.gov).

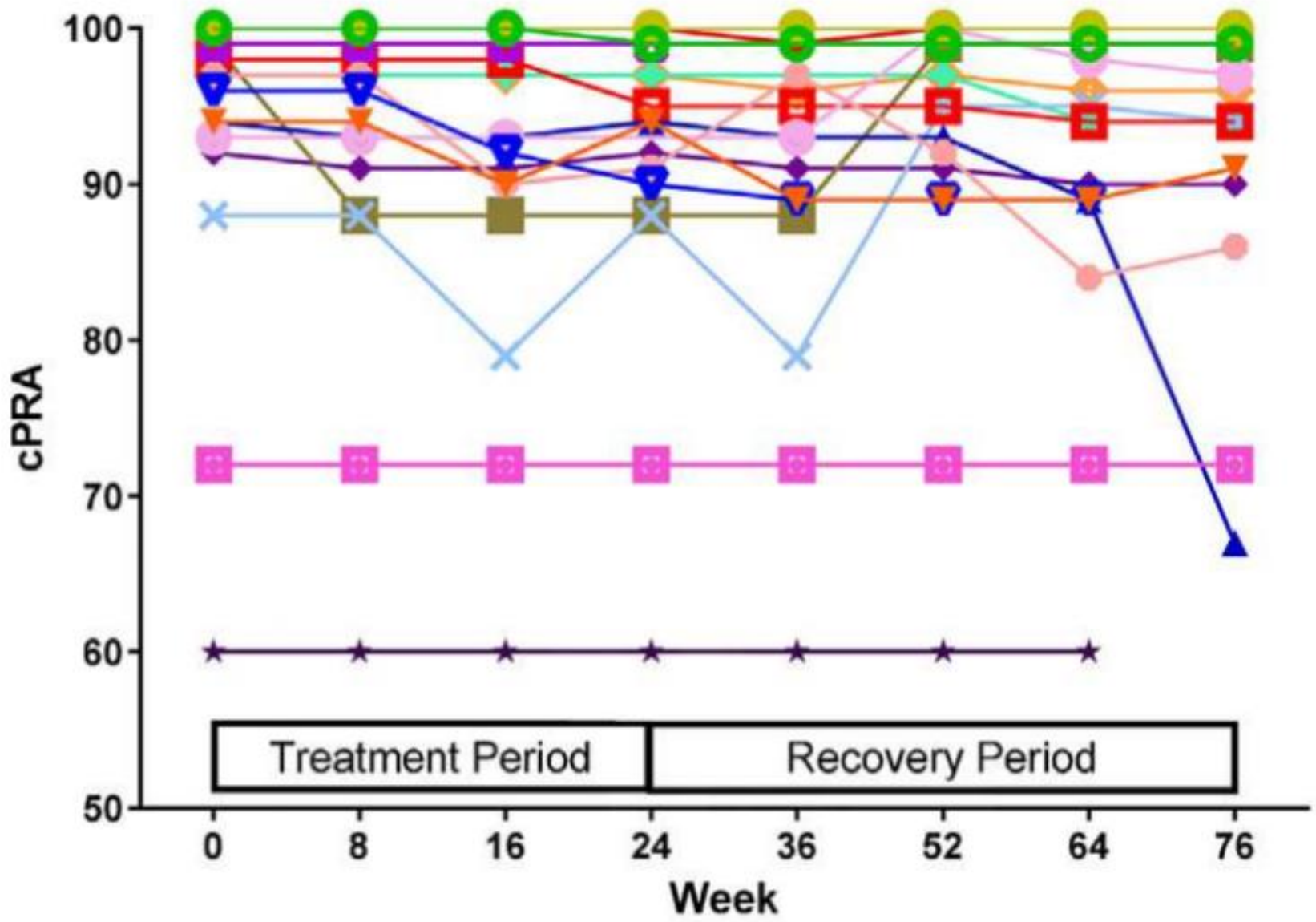
Abbreviations: AE, adverse event; BAFF, B cell–activation factor; cPRA, calculated PRA; ESRD, end-stage renal disease; IVIG, intravenous immunoglobulin; LLN, lower limit of normal; MFI, mean fluorescence intensity; MHCI, MHC Class I; MHCII, MHC Class II; PRA, panel reactive antibody; TACI, transmembrane activator and cyclophilin ligand interactor; UNOS, United Network for Organ Sharing

Received 22 July 2015, revised 23 September 2015 and accepted for publication 28 September 2015



Abbreviations: D = day; n = number of patients; Q4W = every 4 weeks; SC = subcutaneous injection; V = visit; W = week; TC = telephone call.

American Journal of Transplantation 2016; 16: 1266–1275



Individual patient cPRA values following 24 weeks of Tabalumab treatment and up to 52 additional weeks of follow-up.

American Journal of Transplantation 2016; 16: 1266–1275

Conclusion

BAFF inhibition in the setting of the highly sensitized patient provided only a small and likely clinically irrelevant reduction in the cPRA.

TABLE 2 | Efficacy of belimumab, tabalumab, and atacicept.

		RA			SLE				SS	MS
		Atacicept	**Belimumab**	**Tabalumab**	**Atacicept**	**Belimumab**	**Blisibimod**	**Tabalumab**	**Belimumab**	**Atacicept**
Patient no.		311	415	1,041	47/6	1,353	547	1,124	30	255
Duration		38 weeks	24/48 weeks	52 weeks	9/52 weeks	52–76 weeks	24 weeks	52 weeks	52 weeks	36 weeks
Clinical improvement	Partial Complete No	– – *ACR20*	*ACR20:*in 41% – *ACR50+70*	*ACR20/50/70:*in 70/36/13% – –	in 22.2% in 44.5% worse in 33% stopped	*SELENA–SLEDAI/ BILAG:*in 46.5/58.6% – –	*Proteinurea:*reduced – –	*SRI-4:*in 49.2% – secondary end point	*EULAR:*in 86.7% – –	– – Failed and even worse
B cell depletion efficacy in periphery		Circulating mature B and plasma cells reduced	B cell depletion 16–48%; no depletion of memory B cells and plasma cells	B cell reduction by 18–40%; no depletion of memory B cells	Reduction by 60%; plasma cells depleted	Reduction by 55.7%	Significant reduction	Significant reduction	Significant reduction	Significant reduction
Autoantibody involvement		RF but not anti-CCP levels reduced	Reduction of RF by 30%	CRP reduced		Reduction of anti-dsDNA aab by 44–49%	Anti-dsDNA decreasedC3 increased	Anti-dsDNA aab significantly decreased	Reduction of RF by 30%	
Remark		Serum IgA+M (by 19.4%) and IgG (by 8.6%) modestly reduced	Moderate change of total Ig; better response in RF+ or ACPA+ patients	Total serum Ig decline by 11% Phase III study in RA terminated		Seropositive and highly diseased patients respond better; total serum Ig modestly reduced by 16%		C3 + C4 increased; total serum Ig reduced; development was stopped	Total Ig not changed	Severe adverse events; higher relapse rate in treated group compared to controls
References		Genovese et al. (170); van Vollenhoven et al. (171)	Stohl et al. (181)	Smolen et al. (168); Greenwald et al. (169)	Dall'Era et al. (176); Lenert et al. (177); Ginzler et al. (178)	Navarra et al. (172); Furie et al. (173)	Furie et al. (175)	Merrill et al. (174)	Mariette et al. (179)	Kappos et al. (180)

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Clinical improvement	Partial	–	*ACR20:*in 41%	*ACR20/50/70:*in 70/36/13%	in 22.2%	*SELENA–SLEDAI/ BILAG:*in 46.5/58.6%	*Proteinurea:*reduced	*SRI-4:*in 49.2%	*EULAR:*in 86.7%	–
	Complete	–	–	–	in 44.5%	–	–	–	–	–
	No	*ACR20*	*ACR50+70*	–	worse in 33%	–	–	secondary end point	–	Failed and even worse
				–	stopped	–			–	
B cell depletion efficacy in periphery		Circulating mature B and plasma cells reduced	B cell depletion 16–48%; no depletion of memory B cells and plasma cells	B cell reduction by 18–40%; no depletion of memory B cells	Reduction by 60%; plasma cells depleted	Reduction by 55.7%	Significant reduction	Significant reduction	Significant reduction	Significant reduction
Autoantibody involvement		RF but not anti-CCP levels reduced	Reduction of RF by 30%	CRP reduced		Reduction of anti-dsDNA aab by 44–49%	Anti-dsDNA decreasedC3 increased	Anti-dsDNA aab significantly decreased	Reduction of RF by 30%	
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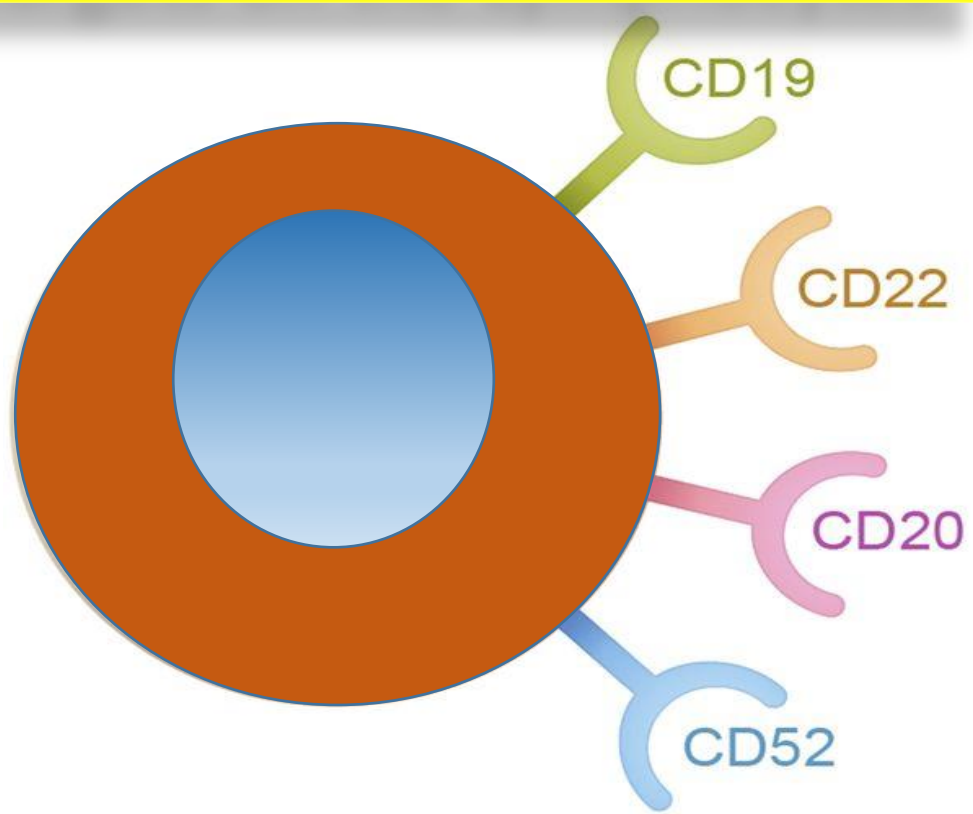
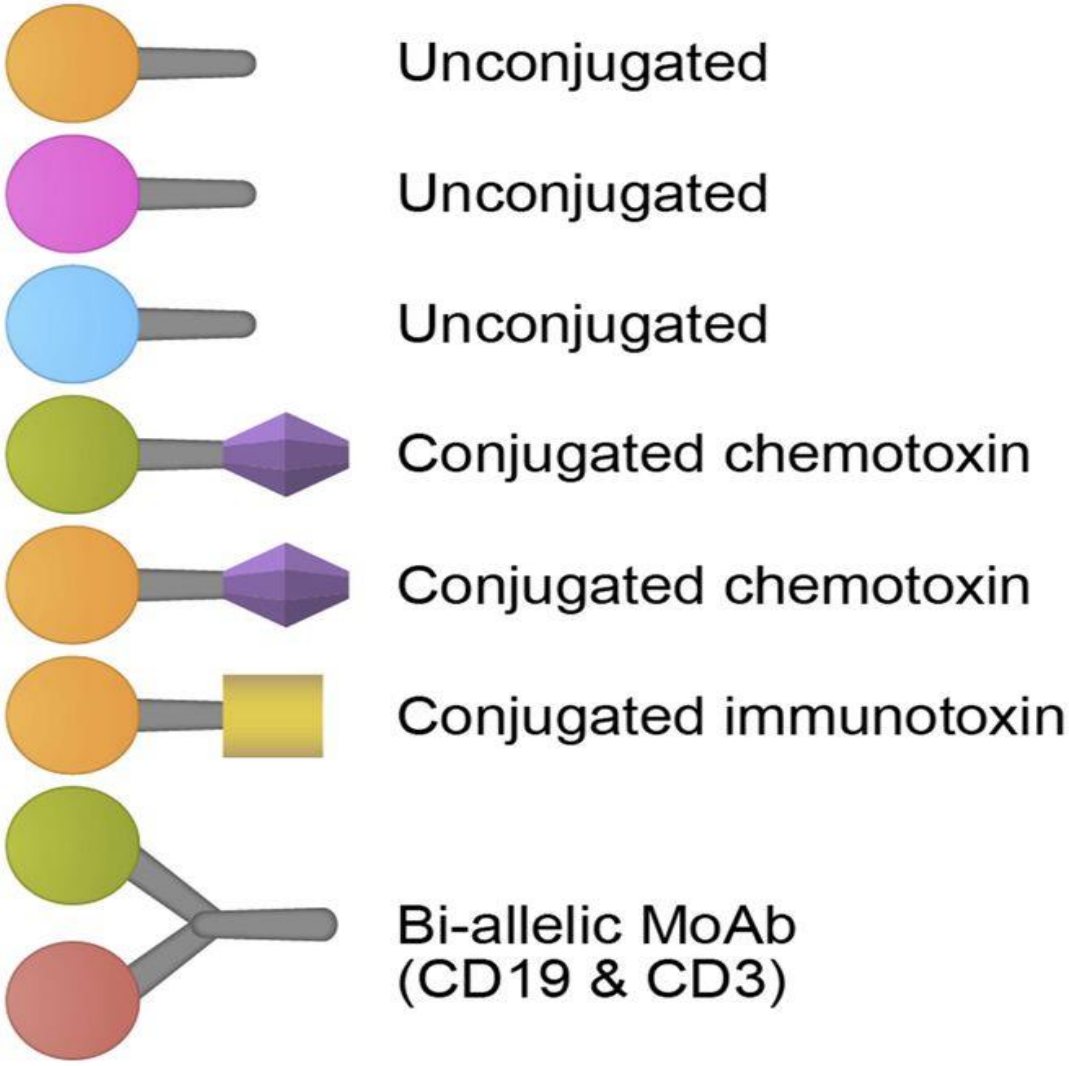
CD Targets on the Lymphocytes





Unconjugated: *Rituximab, Ofatumumab, Obinutuzumab, Epratuzumab, Alemtuzumab*

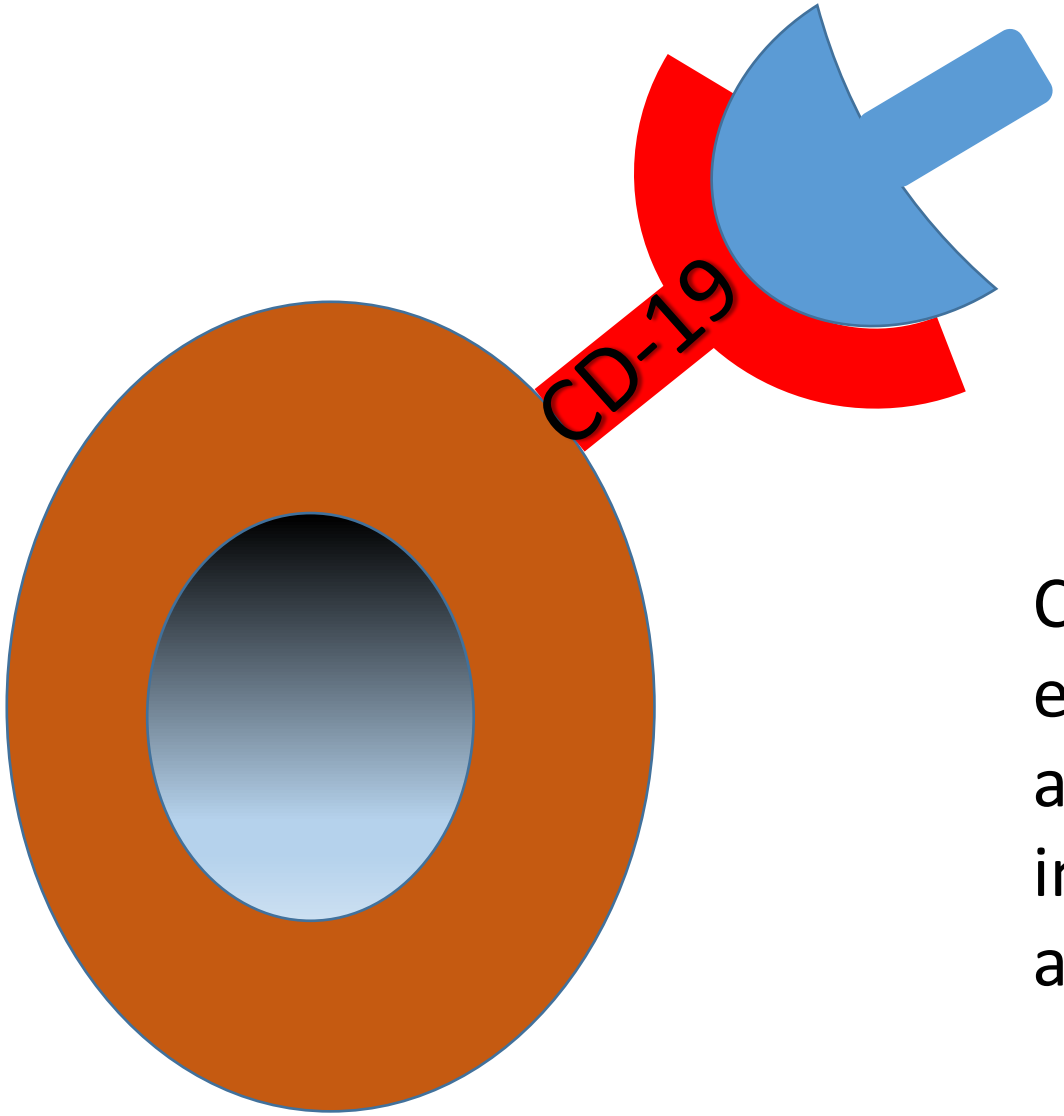
Chemotoxin: *Calicheamicin, Maytansine, Auristatin*

Immunotoxin: *Diptheria, Pseudomonas*

Blinatumomab

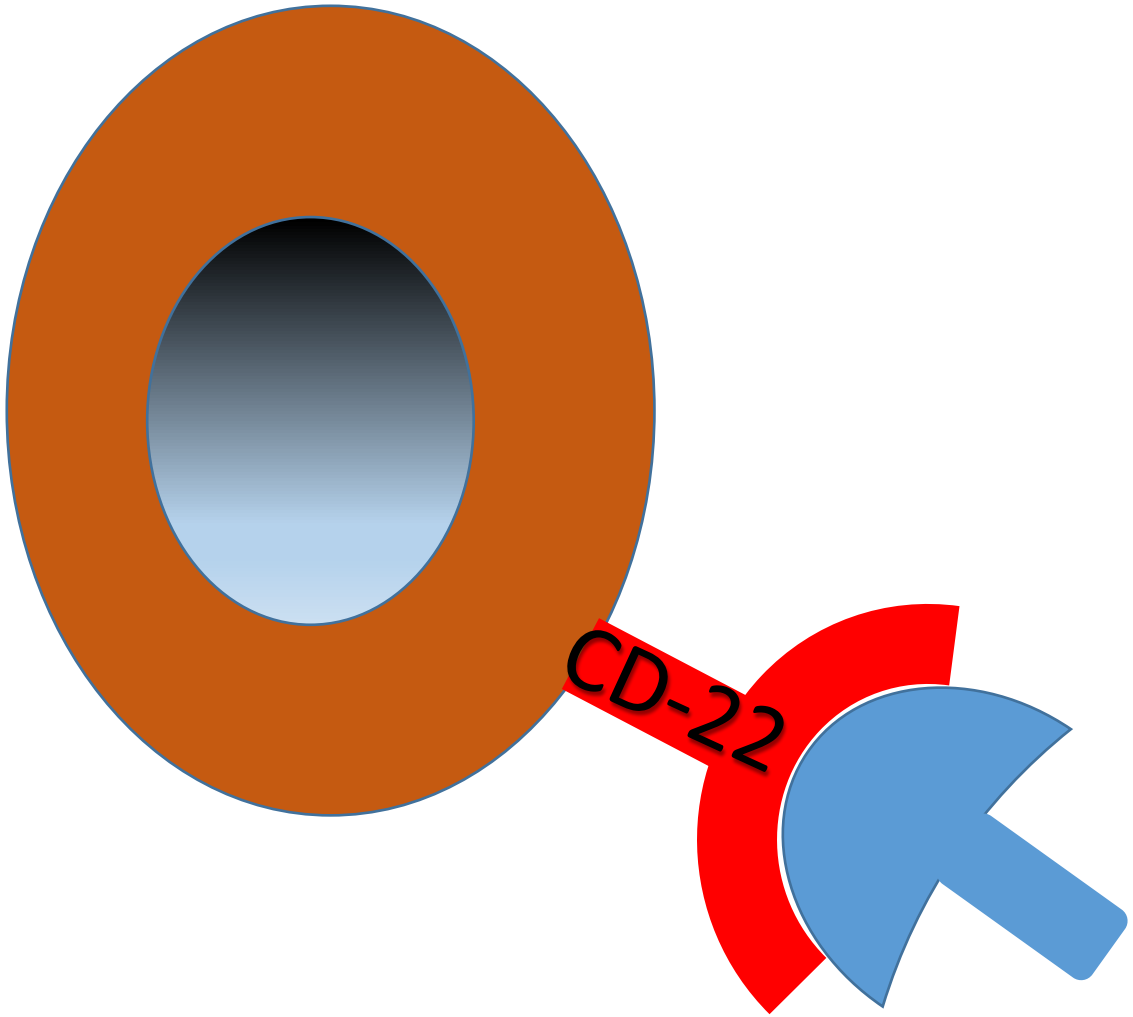
Inebilizumab

SAR3419



CD19 is ubiquitously expressed on B cells. Its expression is continuous from very early stages and throughout differentiation. The antigen internalize on binding of antibody, making it an attractive target for immunoconjugate therapy.

C22 regulates B cell activation for cell cycling differentiation.



Inotuzumab ozogamycin
Epratuzumab

- CD22 is expressed on B cells during B cell maturation and loss of CD20 expression.
- Epratuzumab is a humanized anti-CD22 mAb that inhibits B cell activation and has a more modest depleting effect on B cells than rituximab.
- CD22 is rapidly internalized on antibody binding. Receptor internalization makes it an attractive target for monoclonal antibodies conjugated to cytotoxic compounds.
- Possible mechanisms of action of anti-CD22 antibodies include antibody-dependent cytotoxicity, modulation of B-cell signaling, and inhibition of proliferation.

EXTENDED REPORT

Efficacy and safety of epratuzumab in patients with moderate/severe active systemic lupus erythematosus: results from EMBLEM, a phase IIb, randomised, double-blind, placebo-controlled, multicentre study

Daniel J Wallace,[1] Kenneth Kalunian,[2] Michelle A Petri,[3] Vibeke Strand,[4] Frederic A Houssiau,[5] Marilyn Pike,[6] Brian Kilgallen,[7] Sabine Bongardt,[8] Anna Barry,[7] Lexy Kelley,[7] Caroline Gordon[9,10]

Wallace DJ, et al. Ann Rheum Dis 2014;73:183–190

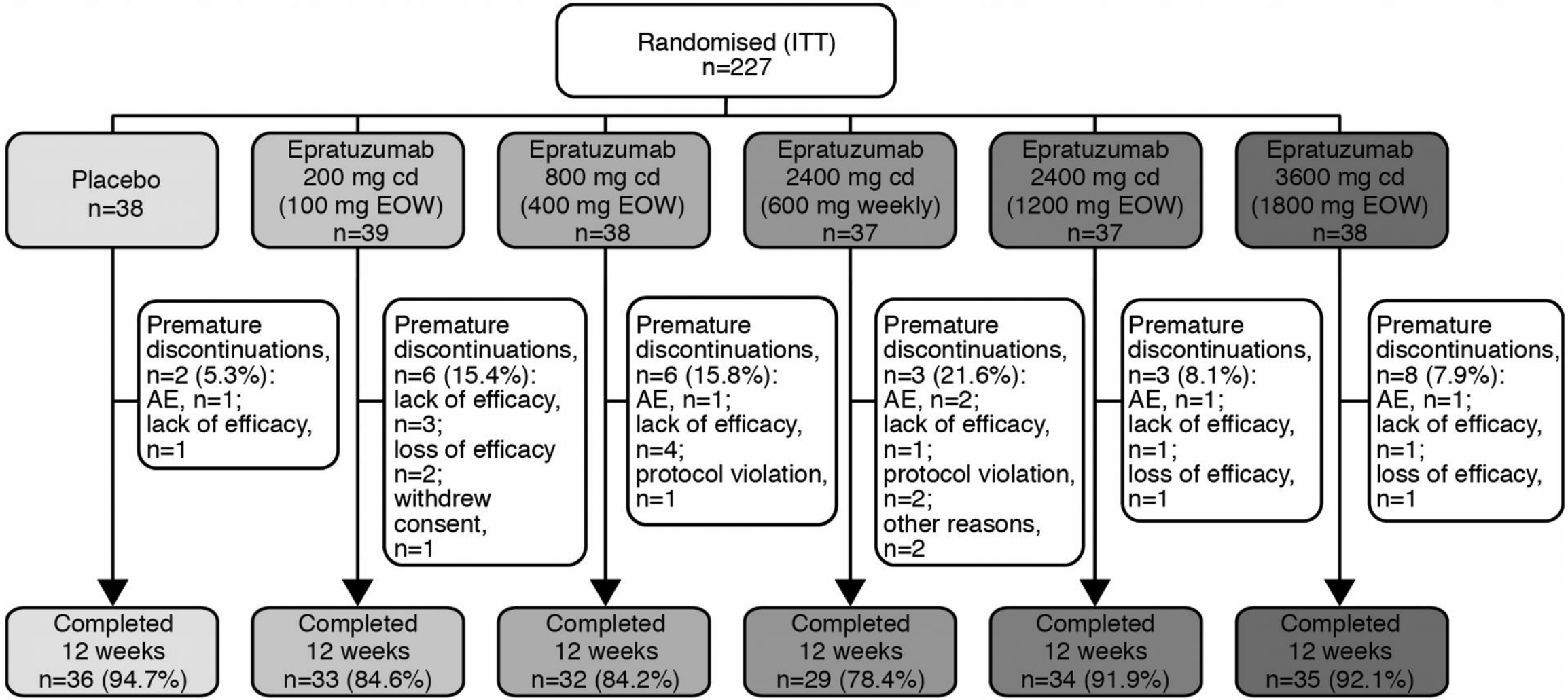
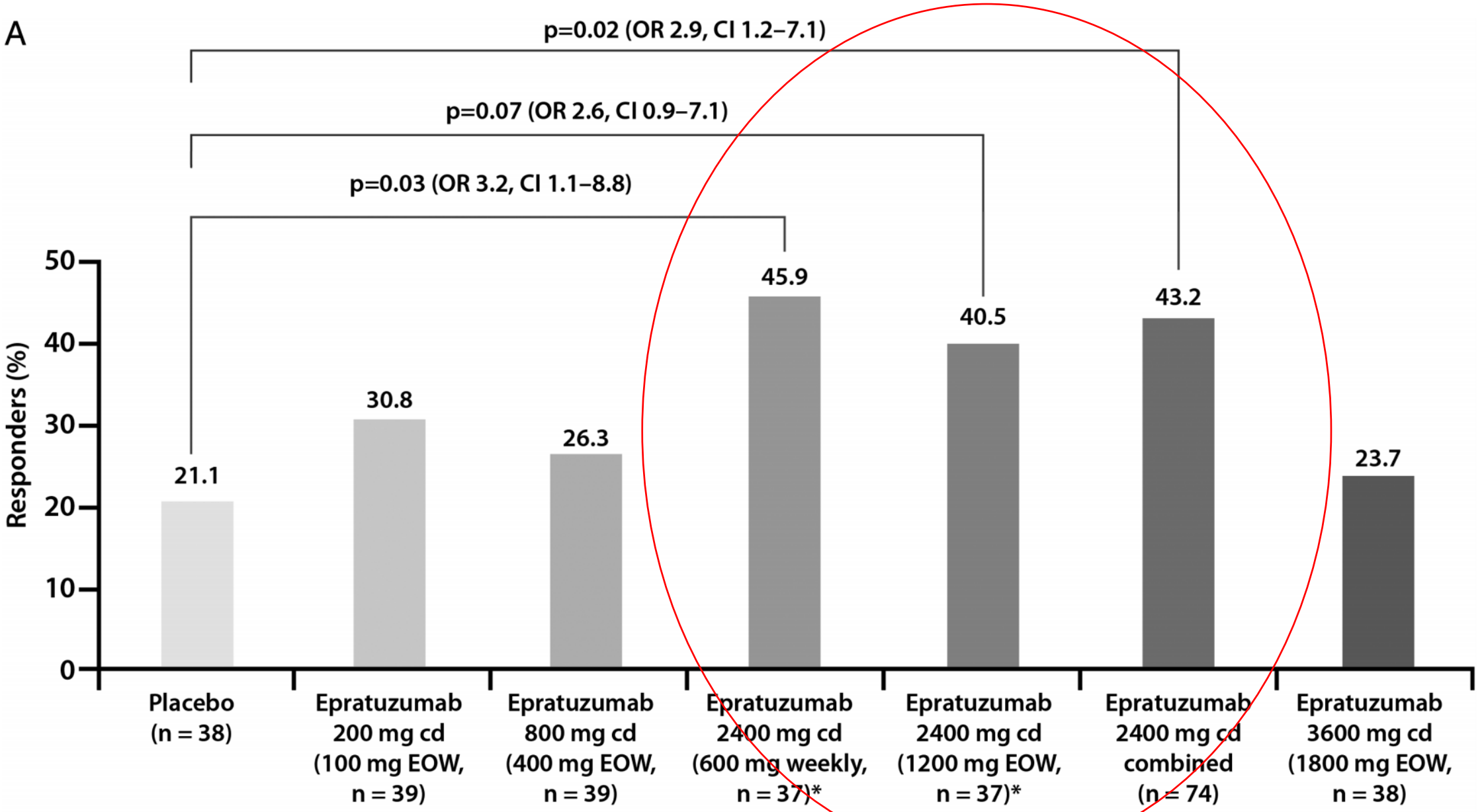


Figure 1 Patient disposition (intention-to-treat population) through EMBLEM.

Wallace DJ, et al. Ann Rheum Dis 2014;73:183–190



Wallace DJ, et al. Ann Rheum Dis 2014;73:183–190

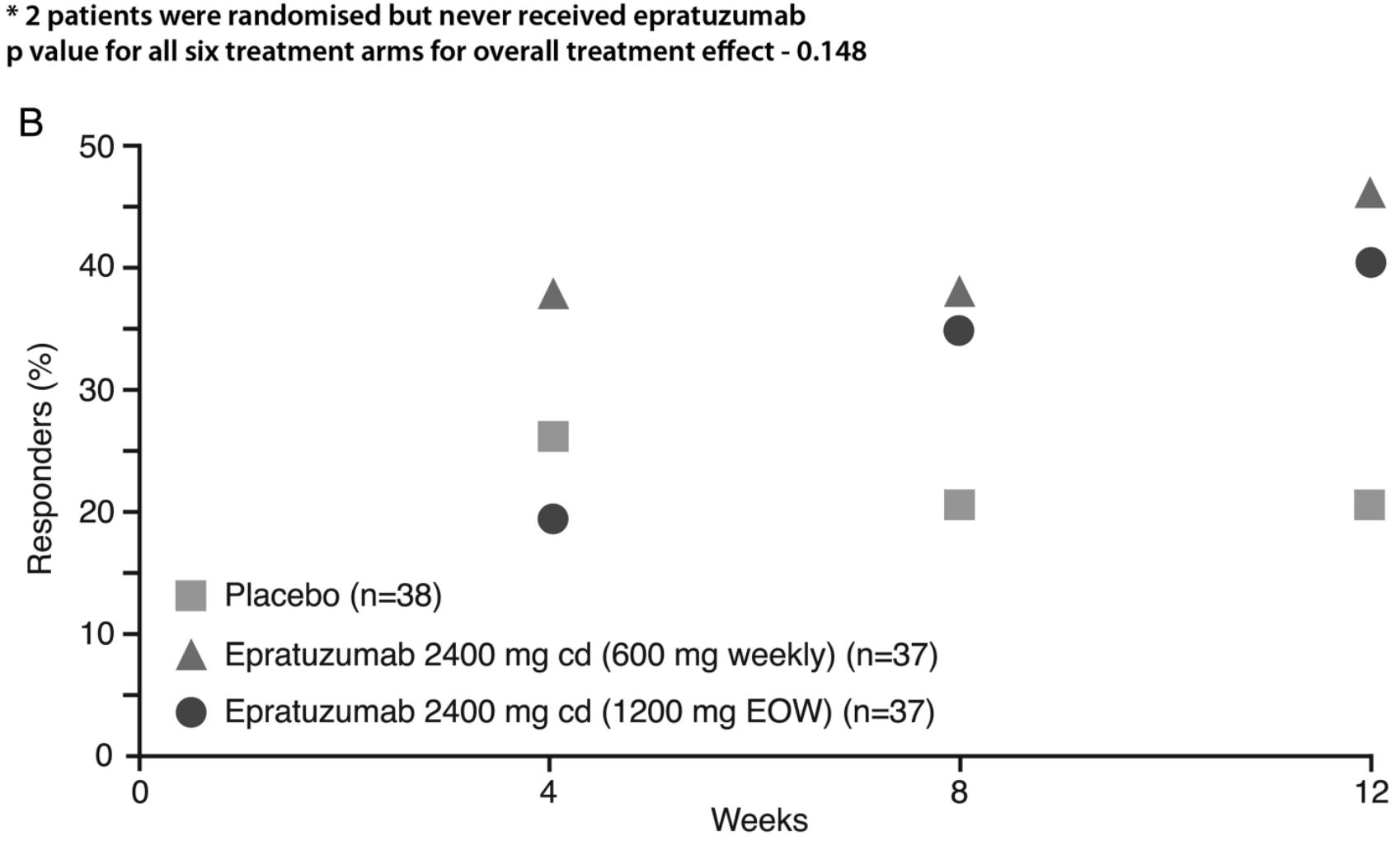
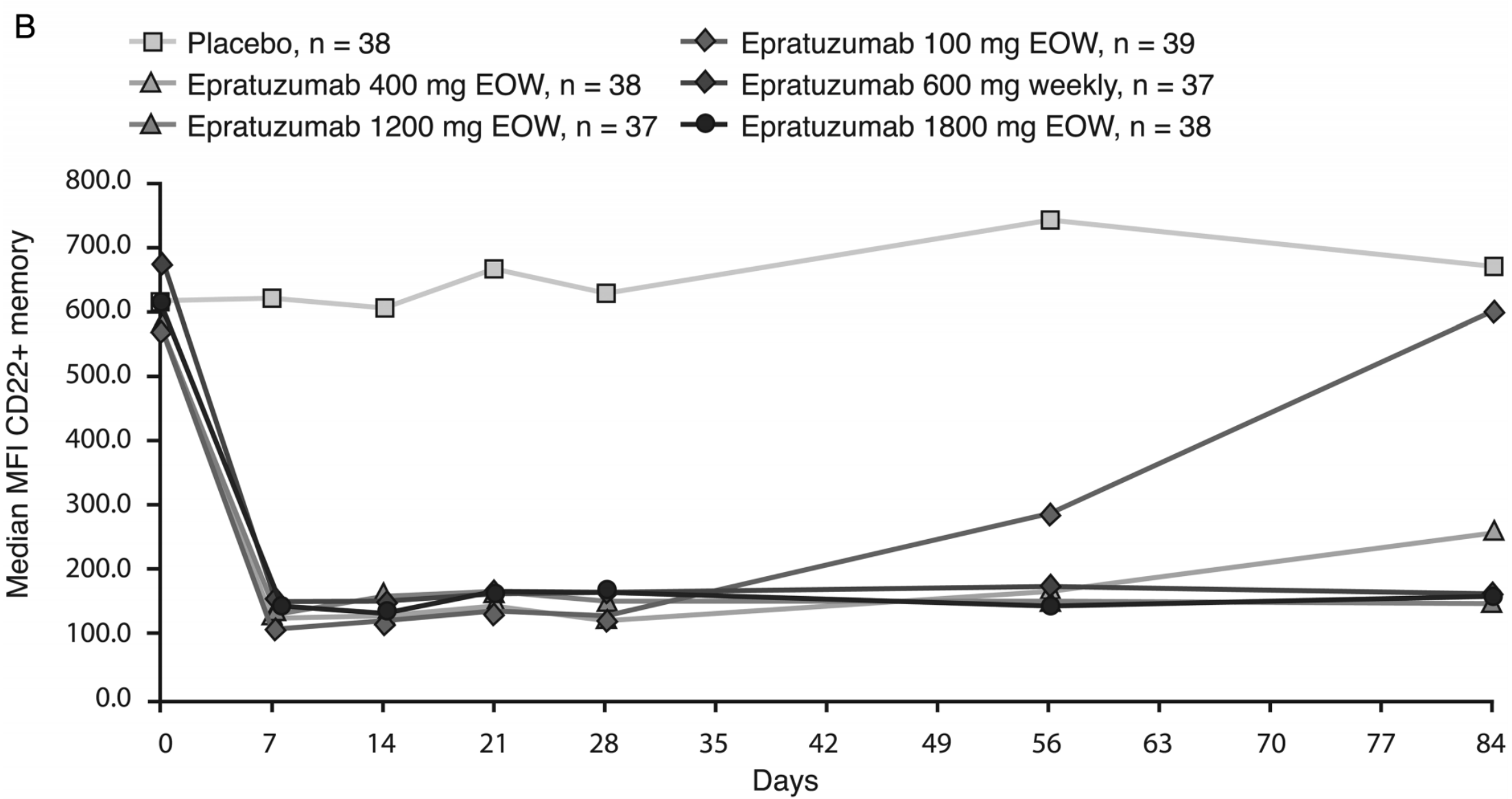


Figure 2 BILAG-based Combined Lupus Assessment response rate (A) at week 12 (intention-to-treat analysis) for all patient groups (B) over weeks 1–12 for the 2400 mg combined dose arms compared with the placebo group.

Wallace DJ, et al. Ann Rheum Dis 2014;73:183–190



Changes from baseline in B-cell and CD22 levels. (A) Changes in absolute B-cell counts (cells/ml) (B) Changes in mean fluorescent intensity of CD22+ memory B cells.

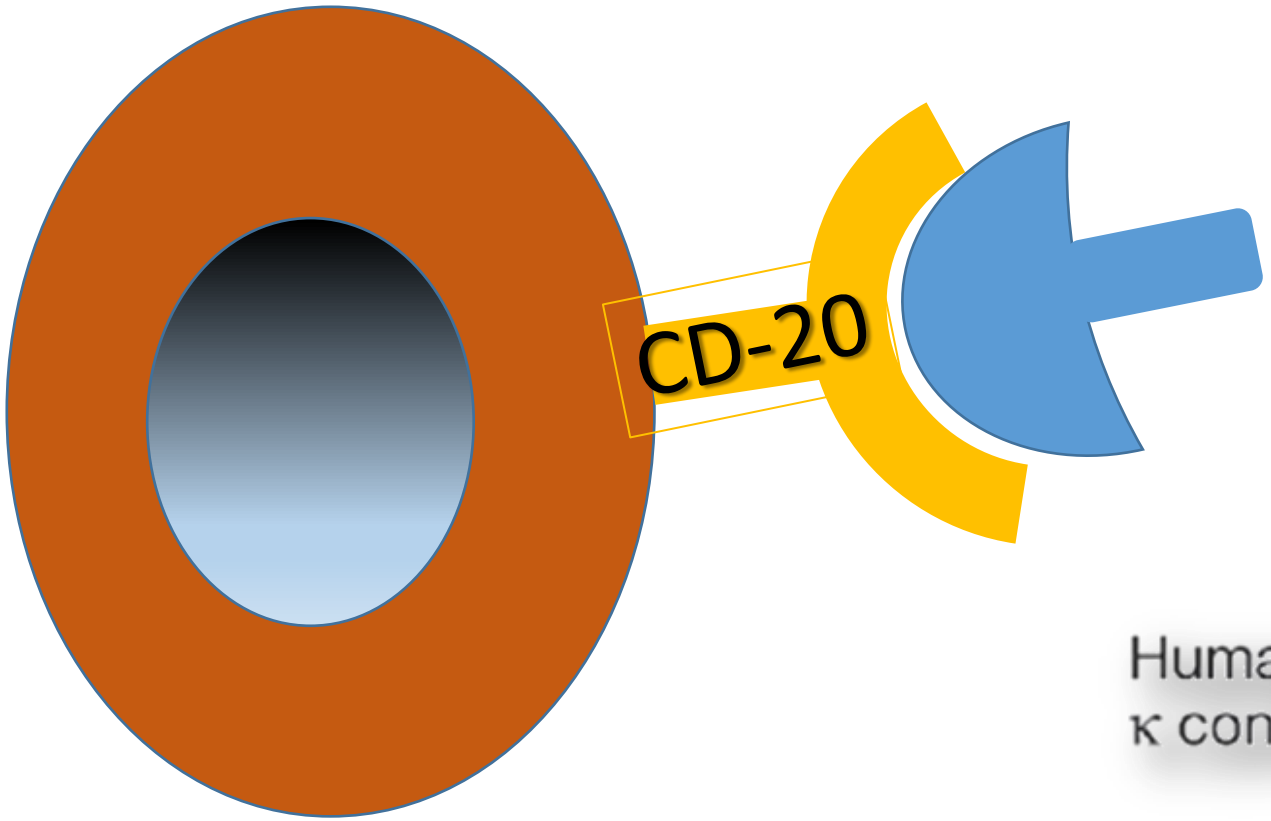
Wallace DJ, et al. Ann Rheum Dis 2014;73:183–190

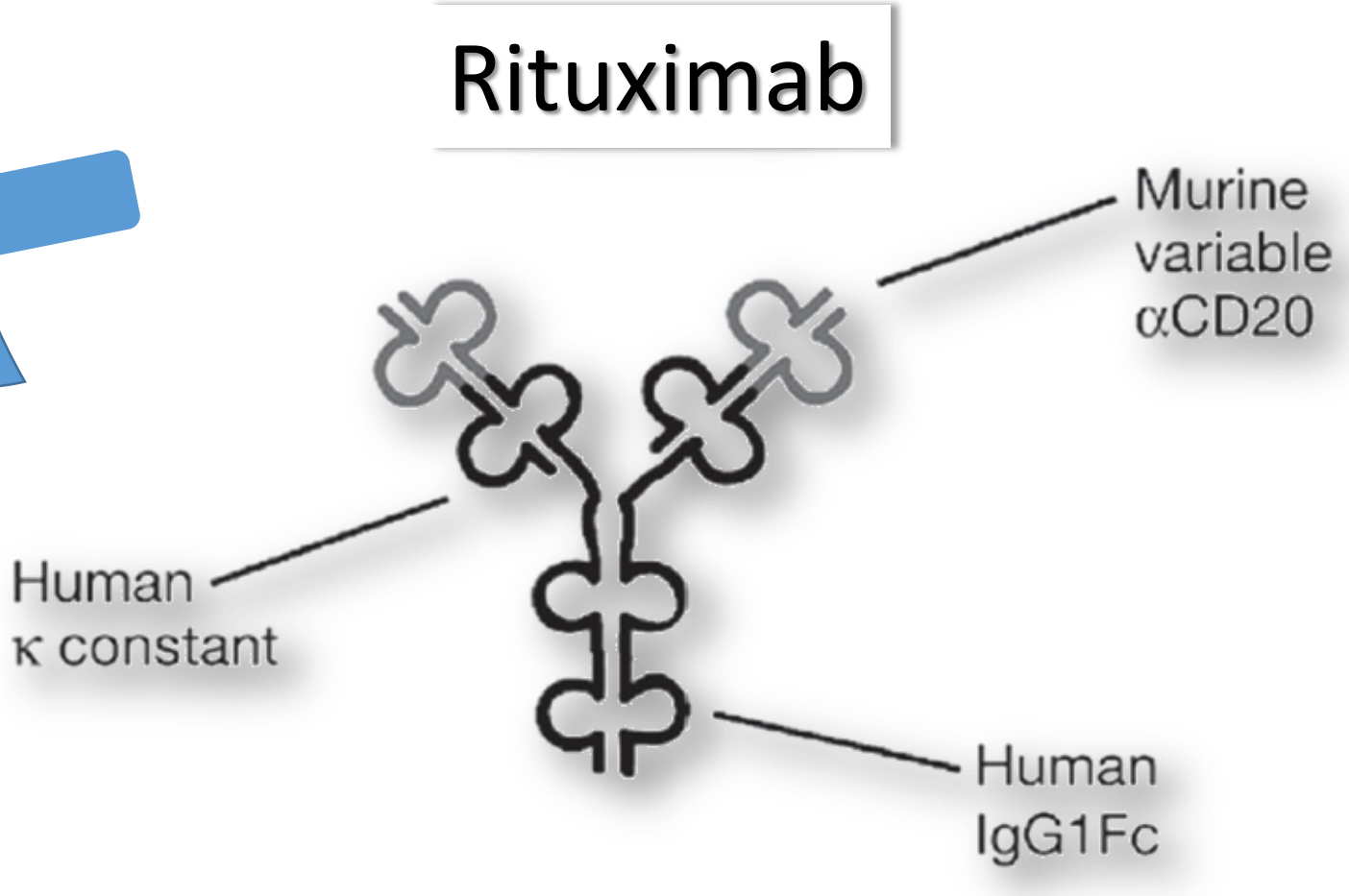
Conclusion

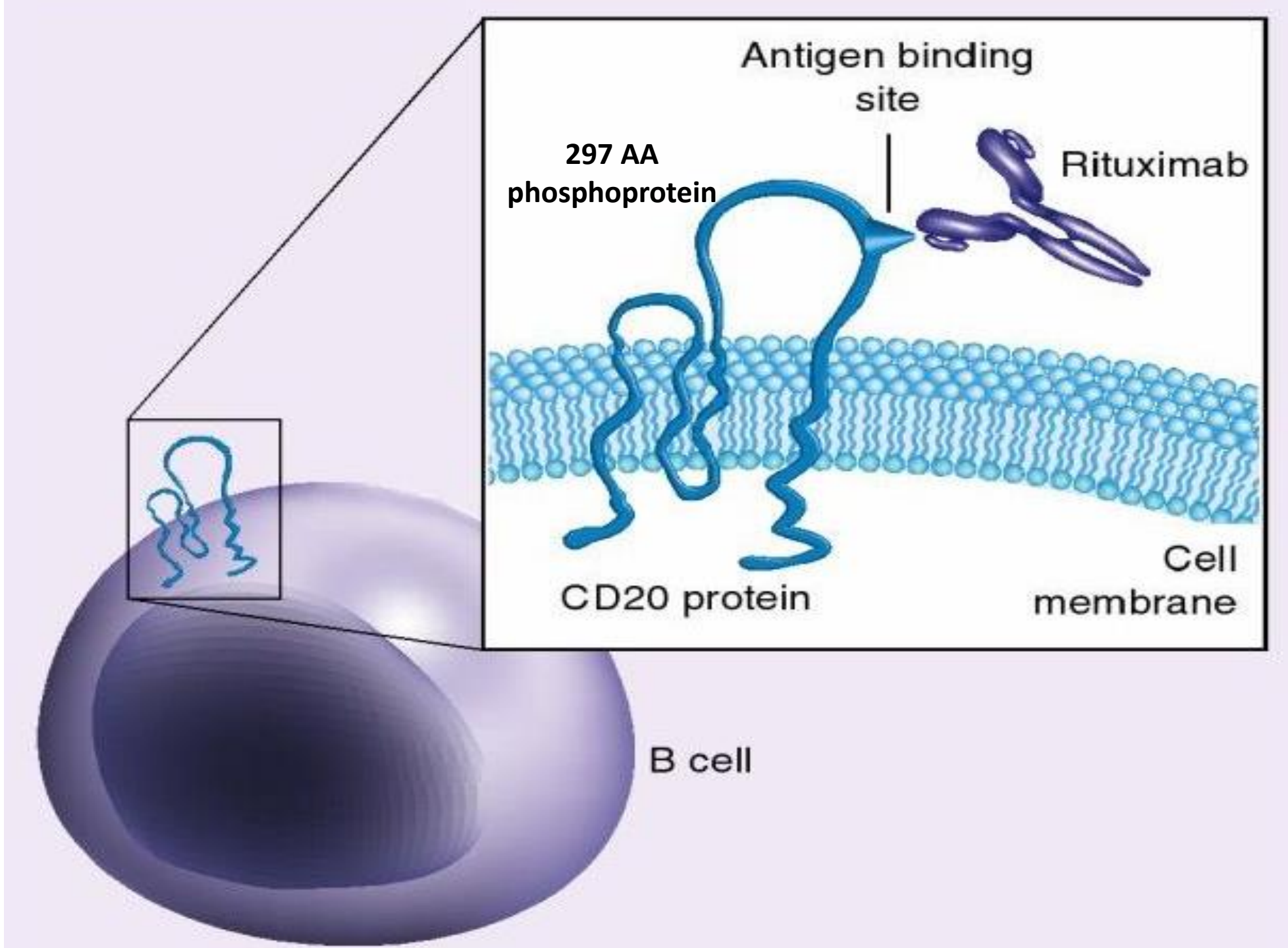
The results of the EMBLEM trial suggest that epratuzumab can improve SLE disease activity, and support continued development of this treatment.

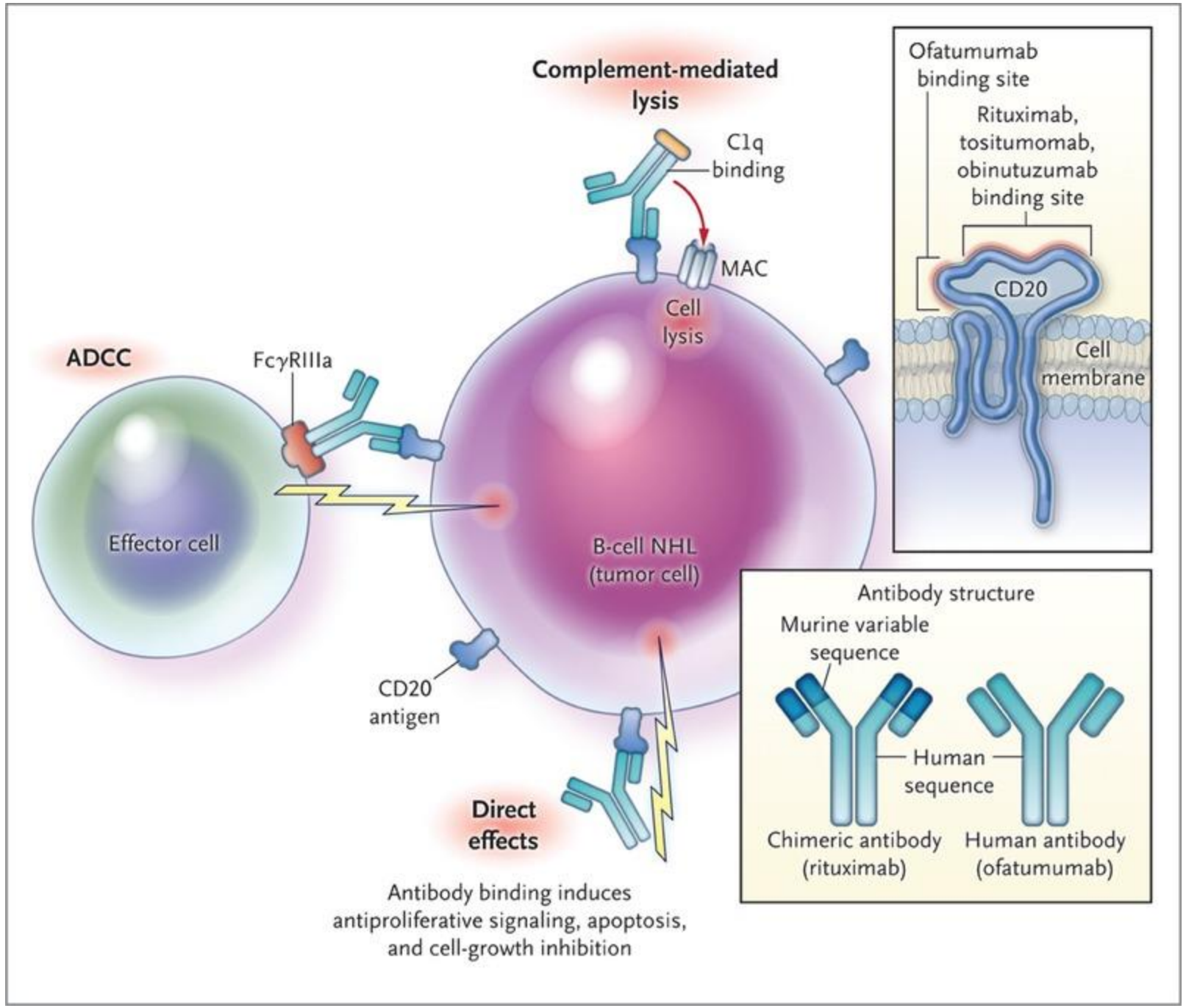
Wallace DJ, et al. Ann Rheum Dis 2014;73:183–190

The role of CD-20 in B cell development includes regulation of activation for cell cycling and B cell differentiation.

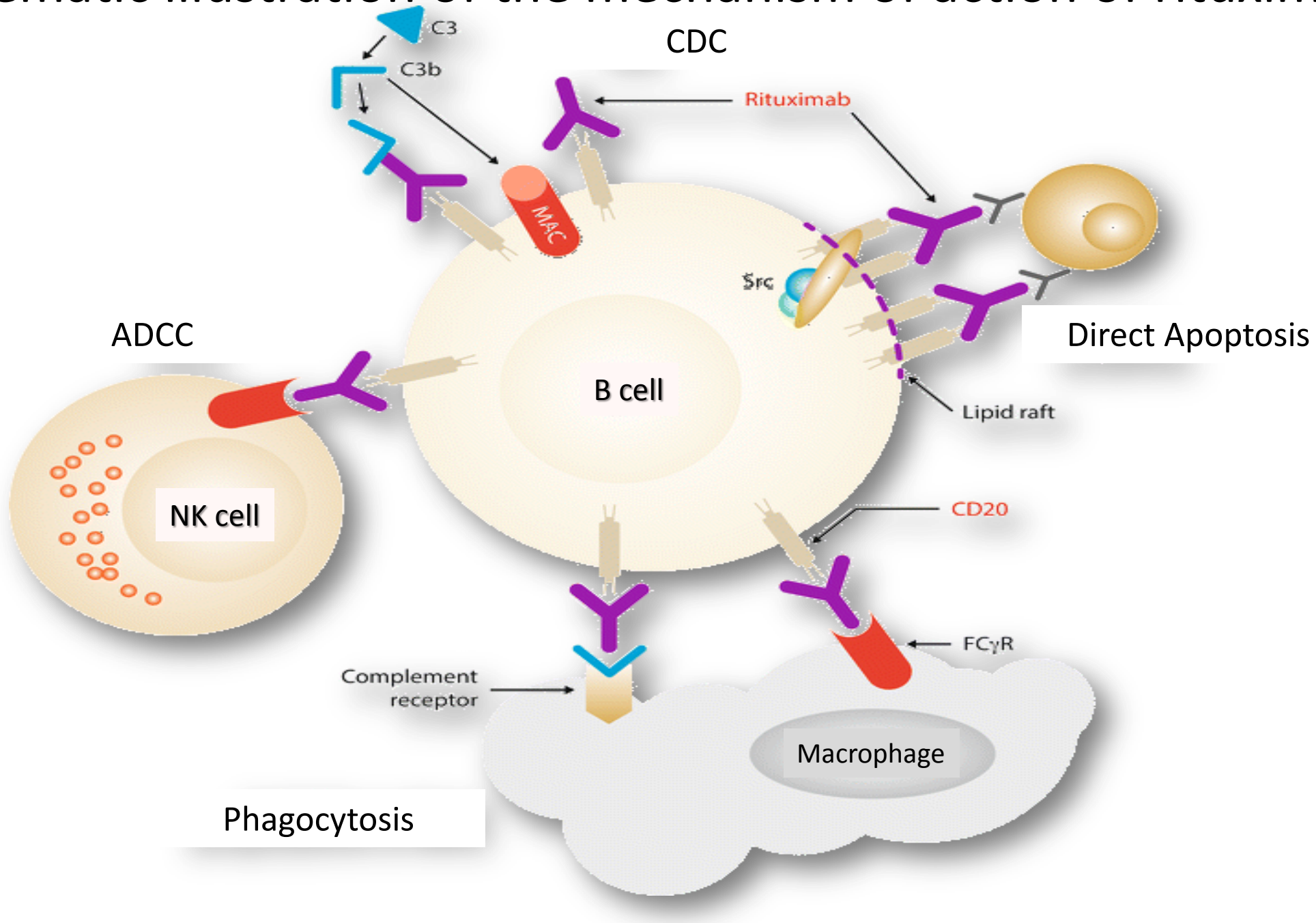




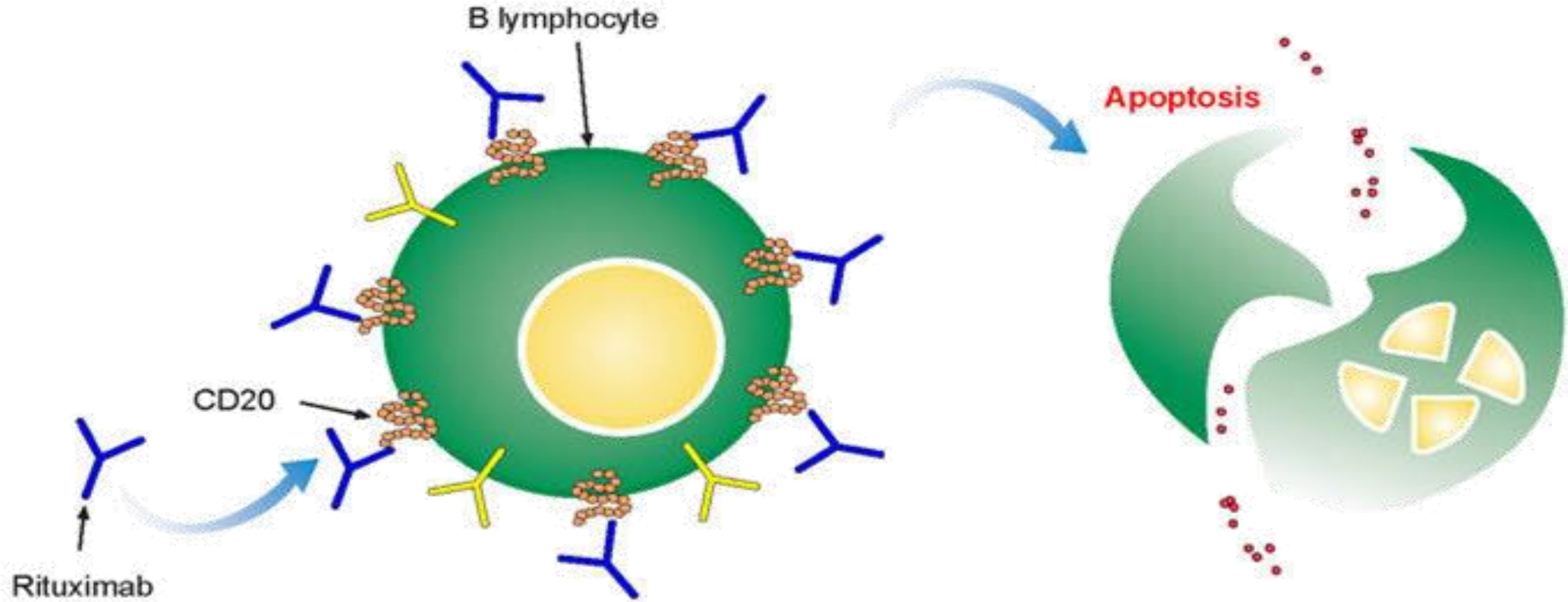

Antigen binding site
297 AA phosphoprotein
Rituximab
CD20 protein
Cell membrane
B cell


Complement-mediated lysis
C1q binding
MAC
Cell lysis
ADCC
FcγRIIIa
Effector cell
B-cell NHL (tumor cell)
CD20 antigen
Direct effects
Antibody binding induces antiproliferative signaling, apoptosis, and cell-growth inhibition
Ofatumumab binding site
Rituximab, tositumomab, obinutuzumab binding site
CD20
Cell membrane
Antibody structure
Murine variable sequence
Human sequence
Chimeric antibody (rituximab)
Human antibody (ofatumumab)

Schematic illustration of the mechanism of action of rituximab

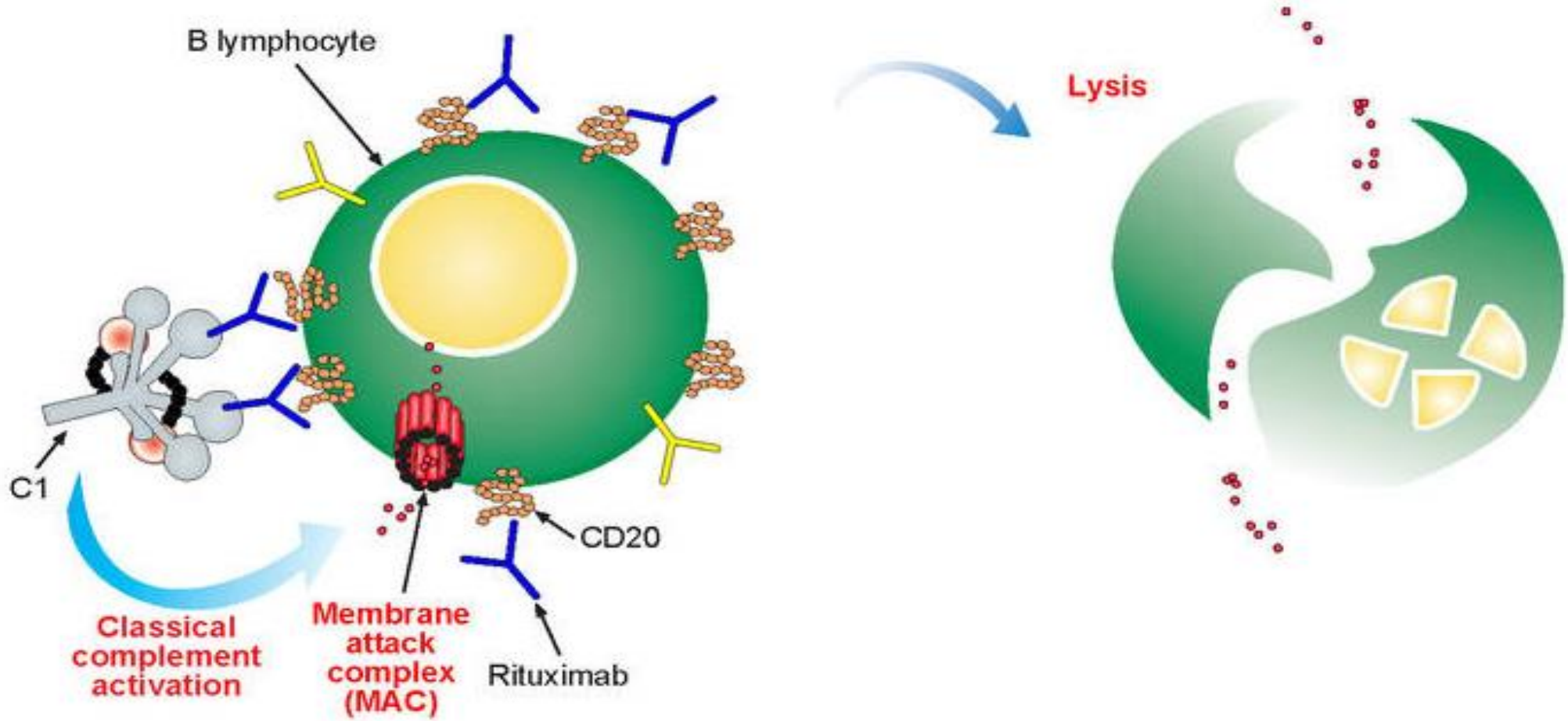


① CD20-induced apoptosis



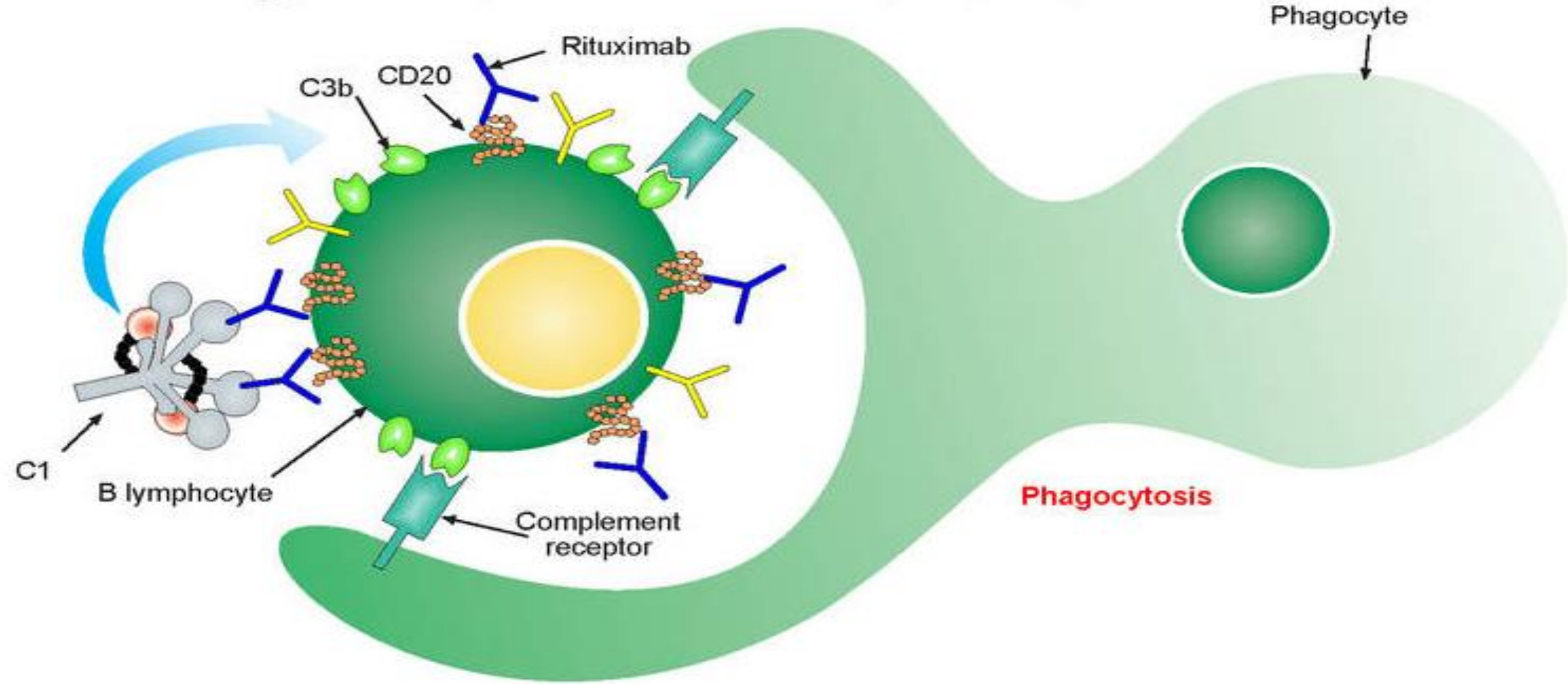
CD20 has an associated intracellular signal transduction mechanism following external receptor stimulation. It has been found that binding of Rituximab to CD20 induces the B lymphocyte to enter the apoptotic pathway.

② Classical complement activation



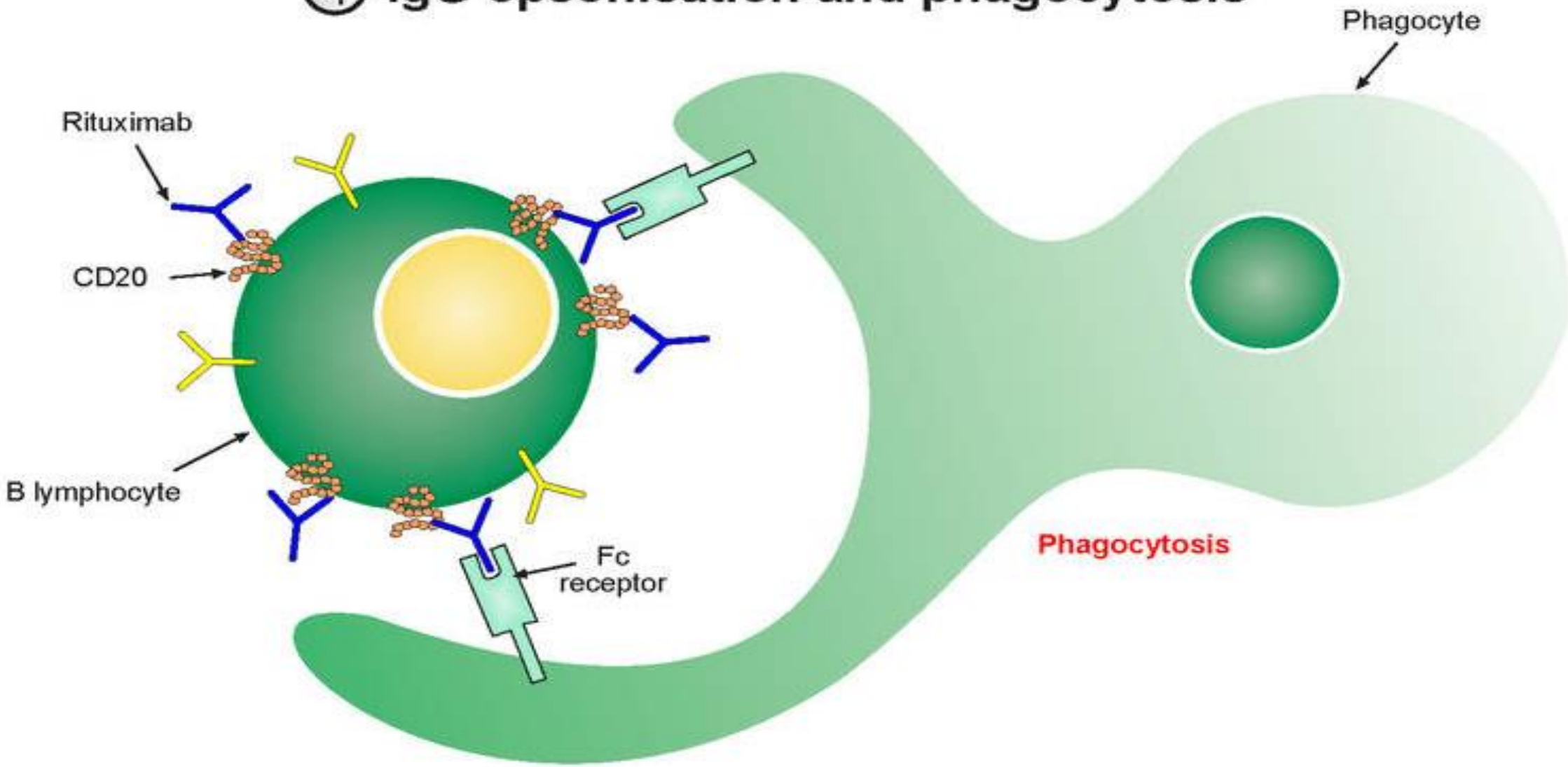
Rituximab is an IgG class antibody that has an Fc portion. After binding to CD20 on B lymphocytes, the Fc portion is able to be bound by complement C1 protein. Binding of C1 activates the classical complement cascade which leads to the formation of the membrane attack complex and cell lysis.

③ C3b opsonisation and phagocytosis



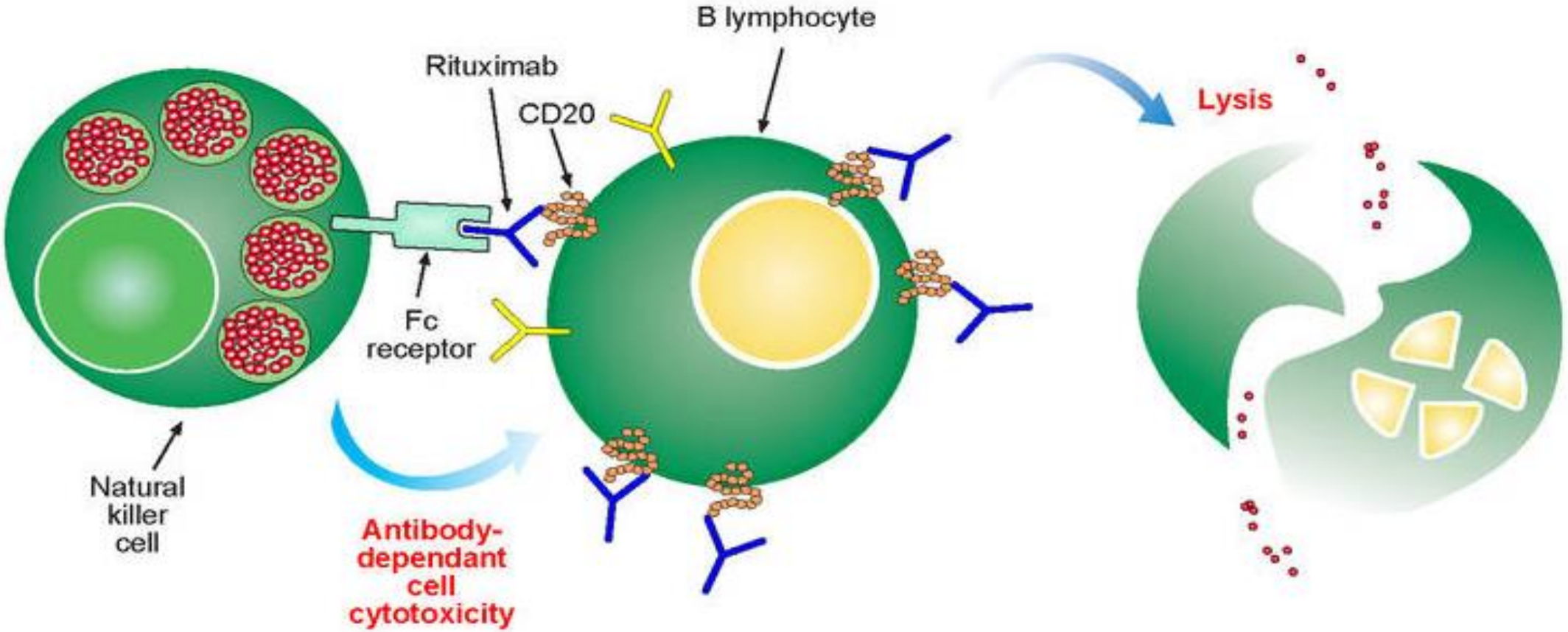
After binding of Rituximab to CD20 on B lymphocytes, complement C1 protein binds to the Fc portion and activates the classical complement cascade. The classical complement cascade generates complement C3b proteins from soluble complement C3 proteins. C3b covalently attaches to the surface of cells and opsonises them. C3b opsonised cells are detectable by complement receptors on phagocytes such as neutrophils, dendritic cells and macrophages. Recognition of C3b opsonised cells by phagocytes induces phagocytosis and destruction of the cell.

④ IgG opsonisation and phagocytosis



Rituximab is an IgG class antibody. Binding of Rituximab to CD20 on B lymphocyte opsonises them with IgG. The Fc portion of the IgG is detectable by Fc receptors on phagocytes such as neutrophils, dendritic cells and macrophages. Recognition of IgG opsonised cells by phagocytes induces phagocytosis and destruction of the cell.

⑤ Antibody-dependent cell cytotoxicity by natural killer cells



Binding of Rituximab to CD20 on B lymphocytes opsonises the cells. Rituximab is an IgG class antibody which has a Fc portion detectable by Fc receptors on natural killer cells. Recognition of IgG opsonised cells by natural killer cells induces degranulation and lysis of the cell by antibody-dependent cell cytotoxicity (ADCC).

CD-20 Abs

Obinutuzumab

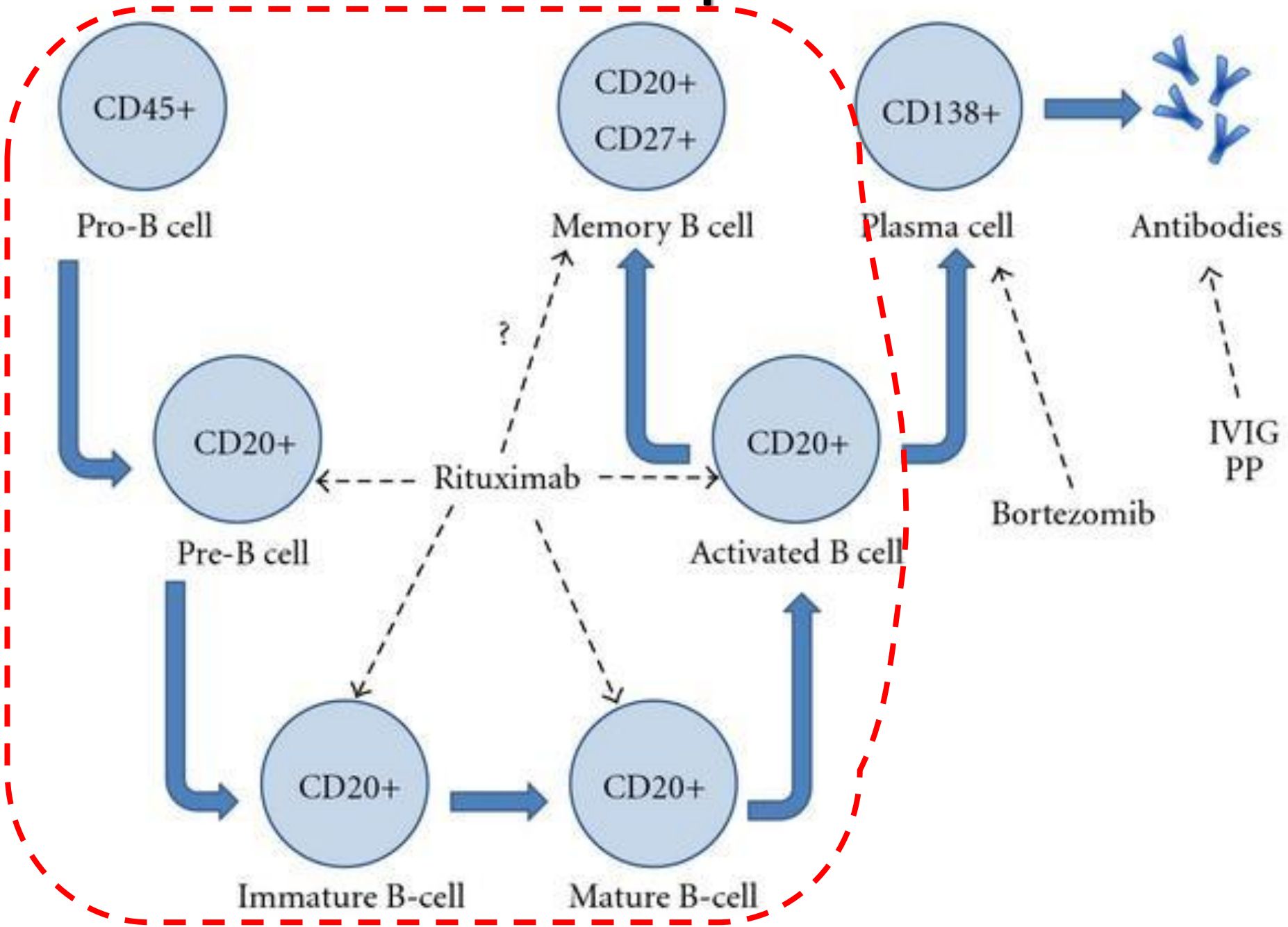
Is a novel glycoengineered type II CD20 monoclonal antibody that is superior to rituximab and ofatumumab in the induction of direct cell death

Ofatumumab

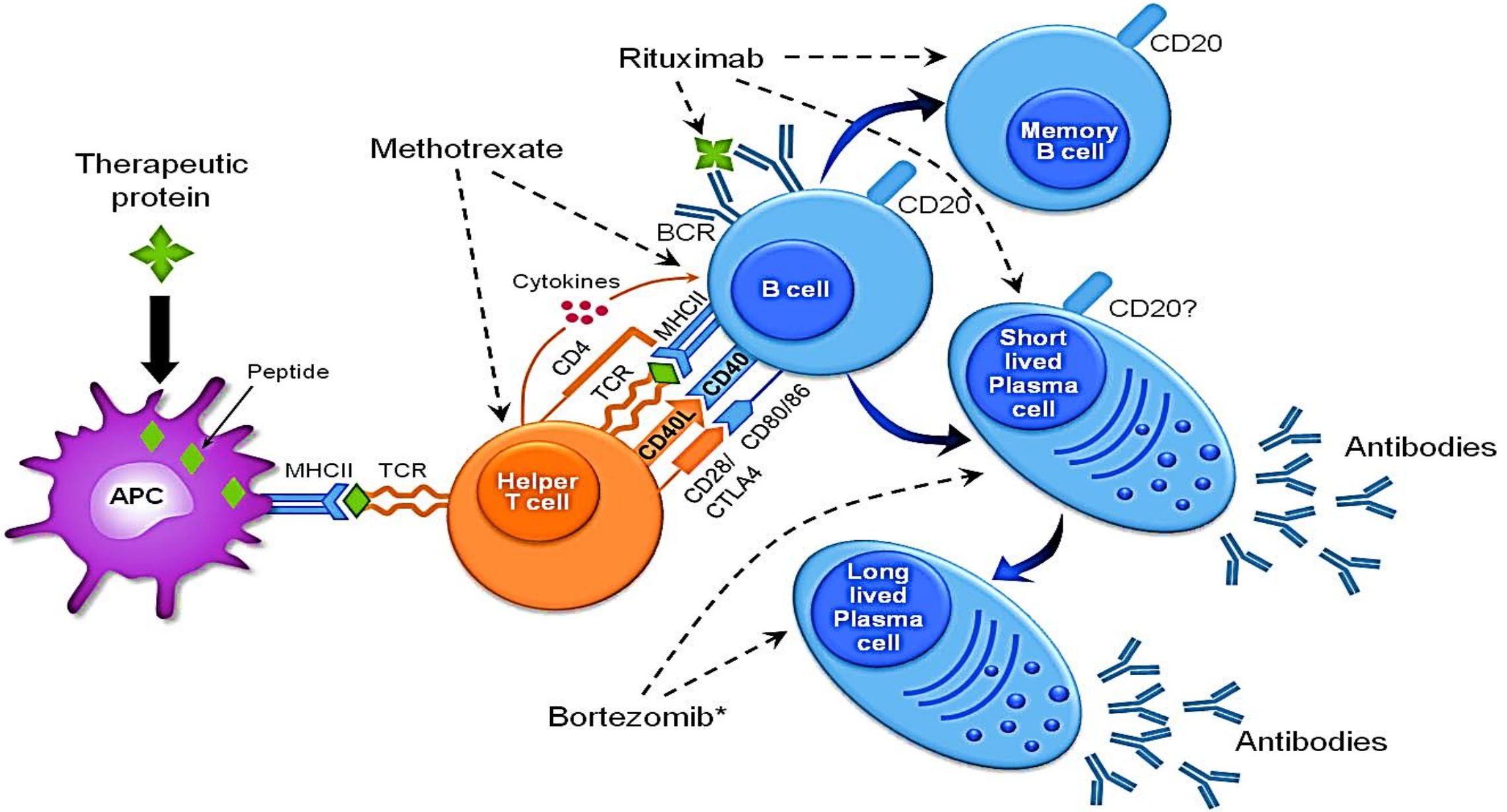
Ofatumumab is a second-generation anti-CD20 monoclonal antibody that binds to a site different than rituximab. targets a membrane proximal small-loop epitope on the CD20 molecule and is more potent than rituximab

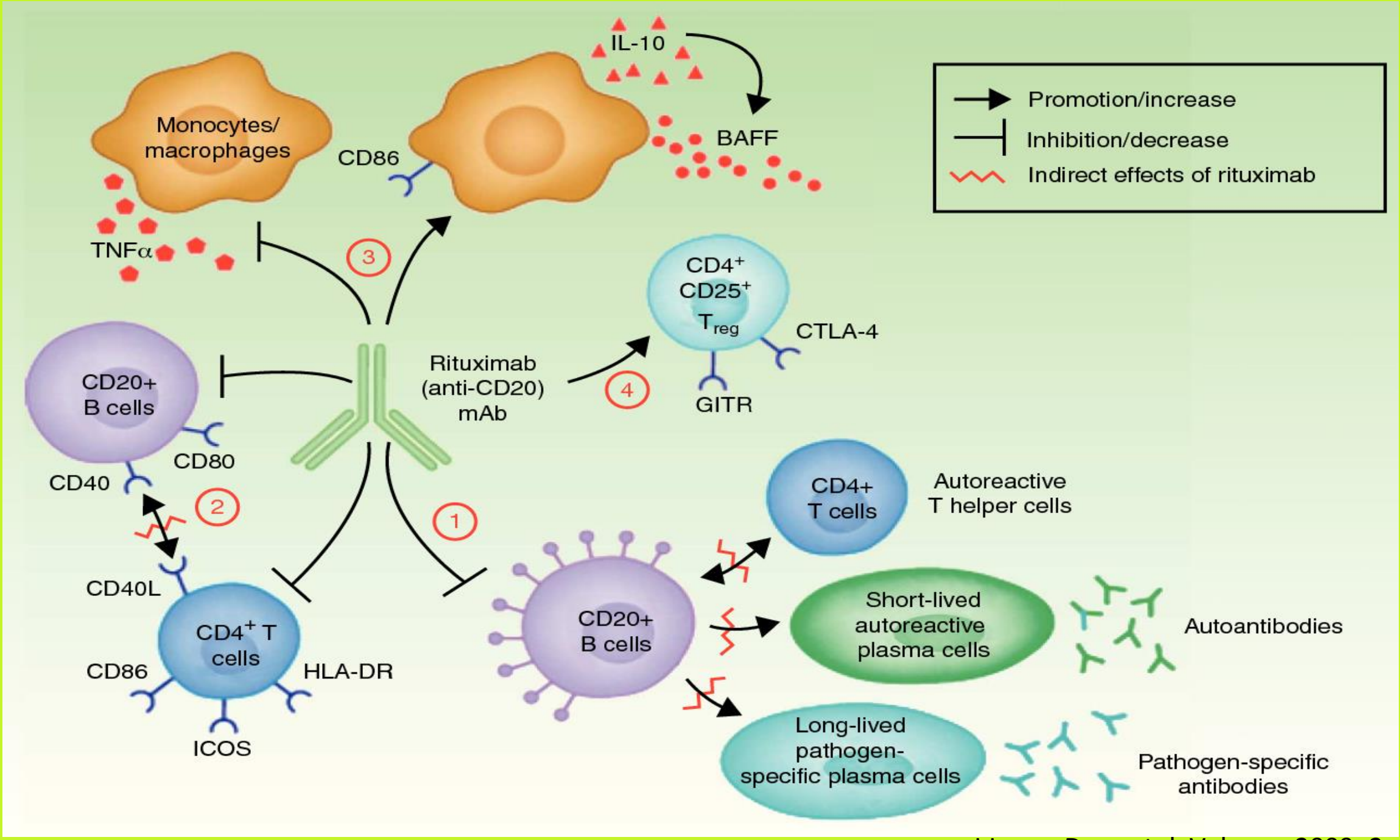
Rituximab

Effect of Rituximab on specific B cells



Humoral immune response to an Ag, and targets of various immunomodulatory agents





J.Inves. Dermatol. Volume ;2009; 2: 289-301

TABLE 1 | Efficacy of RTX treatment varies.

		RA		SLE		PV	MS		
Reference		Emery et al. (11); Rubbert-Roth et al. (105); Haraoui et al. (119)	Rovin et al. (145)	Leandro et al. (146); Albert et al. (147)	Lu et al. (148)	Ahmed et al. (116); Joly et al. (103); Pfütze et al. (117)	Dunn et al. (150); Cross et al. (104)	Hauser et al. (149)	Hawker et al. (151)
Patient no.		120/346/465	144	24	50	11/21/11	16/399	104	439
Dose and duration		1 mg for 24/48 weeks	1 mg for 52 weeks	1 mg for 6 months	1 mg for 6 months	375 mg/m² for 6 months	375 mg/m²/0.5–1 mg for 6 months	1 mg for 48 weeks	1 mg for 96 weeks
Clinical improvement	Partial Complete No	*ACR20/50/70:* in 54–72/27–48/7–23% – in 5%	*Proteinurea:* in 26.4% in 30.6% in 43.1%	*Proteinurea/BILAG/ SLEDAI:* in 65–70% – –	*BILAG:* in 42% – –	*Skin lesions:* in 8.2–20% in 80–95% –	*EDSS:* in 12.5–63.2% – in 36.8–81.25%: worse in 6.25%	*GELN:* in 80.3% in 19.7% –	*CDP:* – – in 100%
B cell depletion efficacy in periphery		Significant depletion to 6 cells/μL	Complete depletion in 99%	Almost complete depletion in 94–96% of patients	Complete depletion in 42%; partial depletion in 47% and no depletion in 11% of patients	In almost all patients complete B cell depletion	Depletion by 95–99.8% in all patients; 90% depletion in spinal fluid	Over 95% depletion in all patients	
Autoantibody involvement		Anti-CCP aab and RF reduced by 45%	Anti-dsDNA aab reduced by 75%	Anti-dsDNA aab reduced by 35%	Anti-dsDNA aab reduced by 60%	In 81.8% IgG/IgG4 anti-keratinocyte cell-surface aab undetectable; dramatic decrease of IgG/IgG4 anti-Dsg1 (by 80%) and Dsg3 (by 65%) aab	Elevated serum anti-MOG aab	–	
Remark		HACA in 2.3–7.3%	–	HACA in 33%, correlating with B cell depletion rate		Clear correlation between aab and disease	HACA in 24.1–37%, correlates with B cell depletion rate	HACA in 24.1% of patients	

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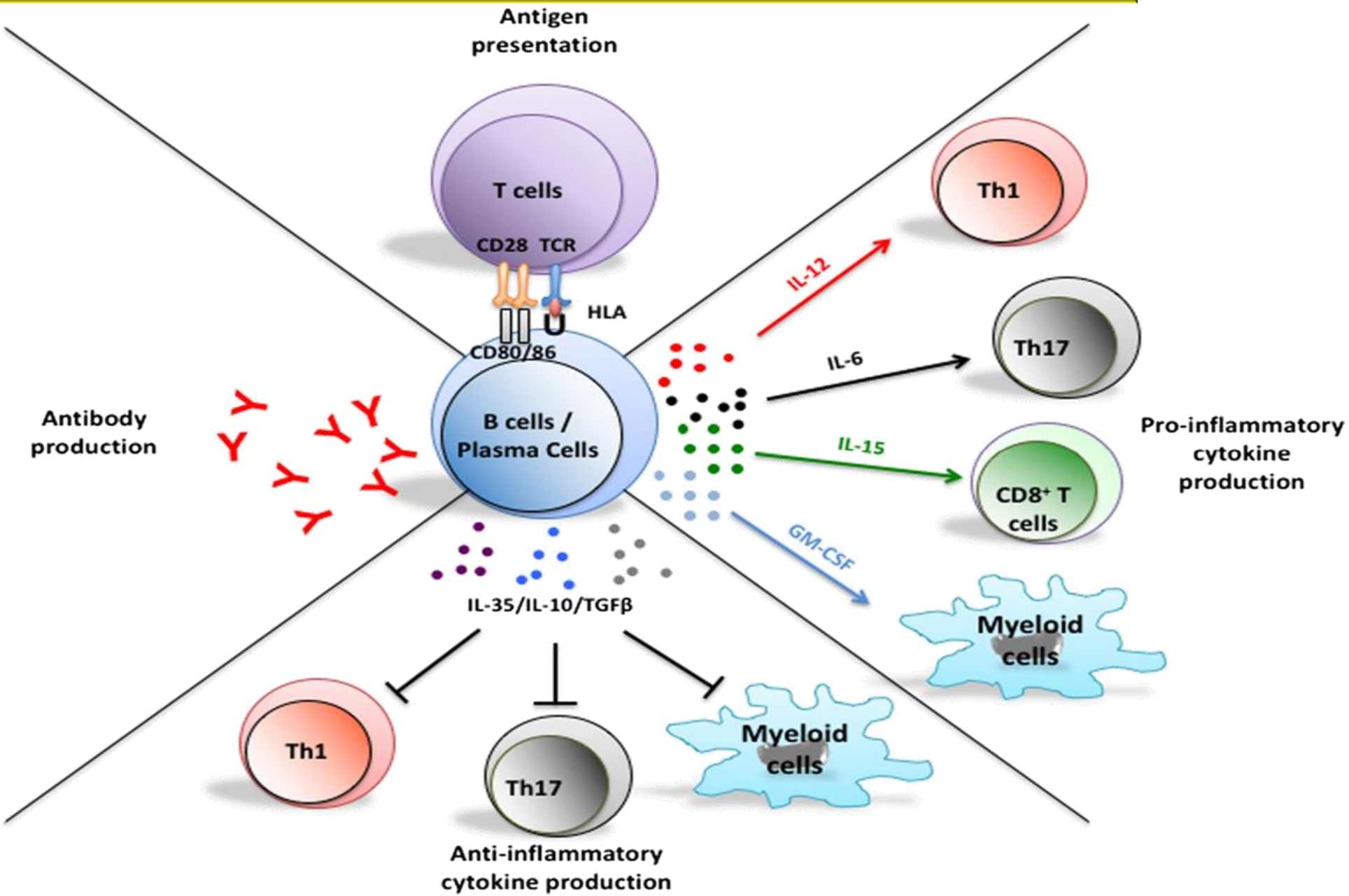
Remark		HACA in 2.3–7.3%	–	HACA in 33%, correlating with B cell depletion rate		Clear correlation between aab and disease	HACA in 24.1–37%, correlates with B cell depletion rate	HACA in 24.1% of patients	

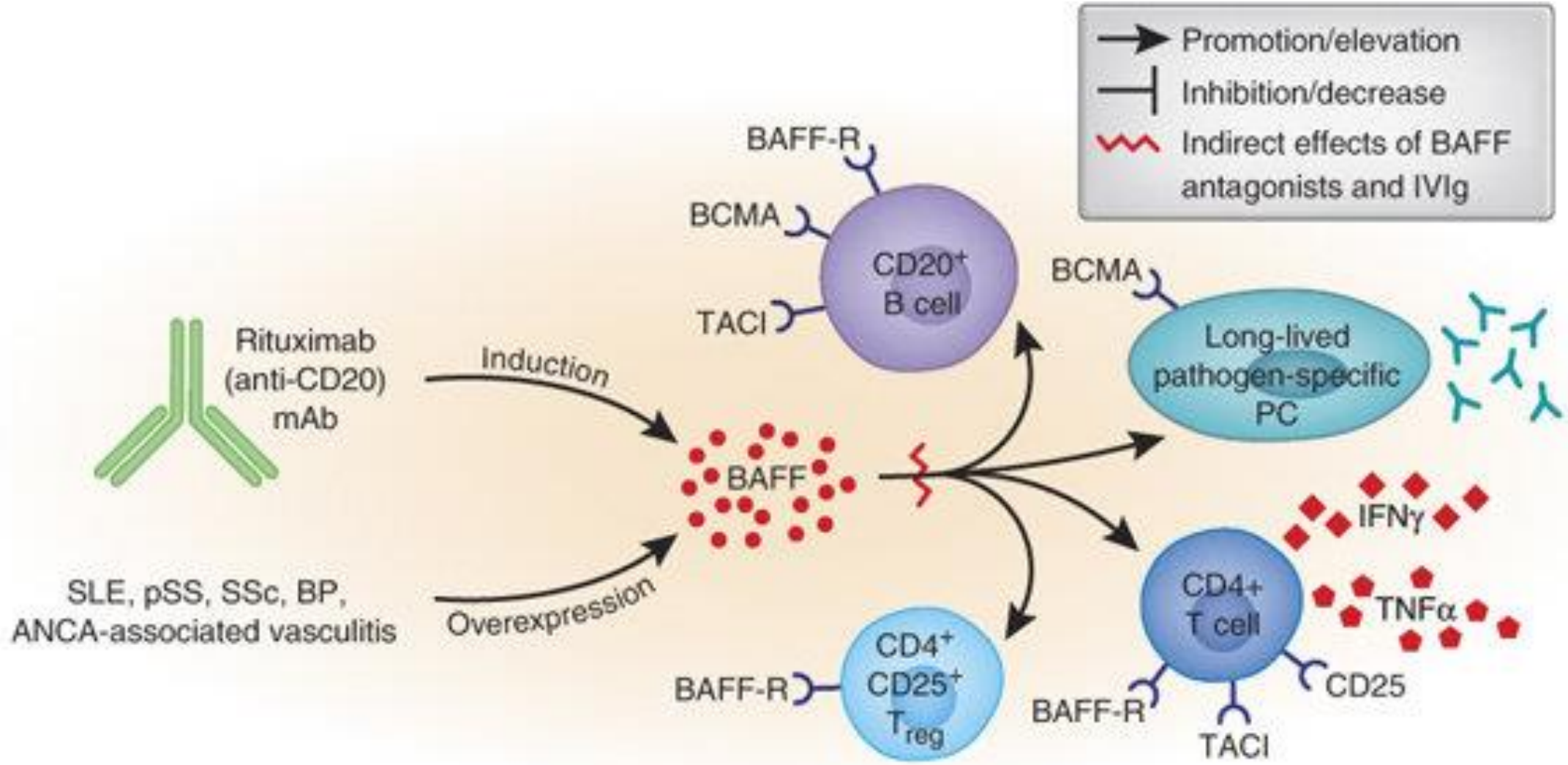
Interleukins released from B cells



Potential mechanisms of resistance or of susceptibility to depletion by anti-CD20 monoclonal antibodies

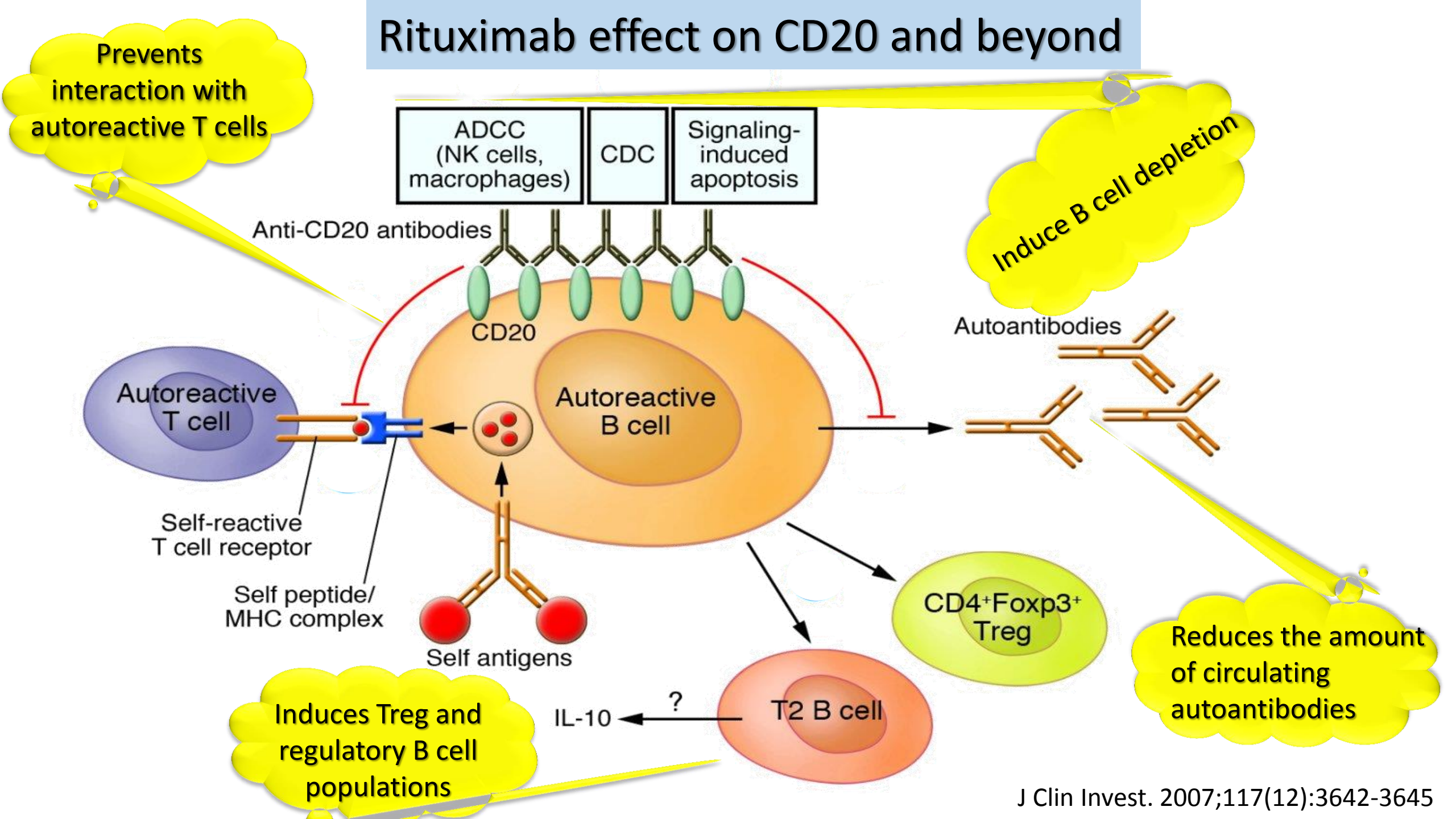
Depletion	Mechanisms
B-cell and antigen related	Lack of CD20 surface expression
	CD20 (antigen) modulation/endocytosis
	Lipid raft composition
	Expression of complement regulatory proteins
Immune host phenomena related	FcγRIIIA polymorphisms
	FcγRIIB expression
	C1q polymorphisms
	Exhaustion of cytotoxic mechanisms (for example, complement)

Rituximab exerts various immune functions by the induction of BAFF



Therapeutic administration of BAFF antagonists or intravenous immunoglobulin (IVIg) interferes with these different effects of BAFF

Rituximab effect on CD20 and beyond



J Clin Invest. 2007;117(12):3642-3645

Comment on Thai et al, page 1545

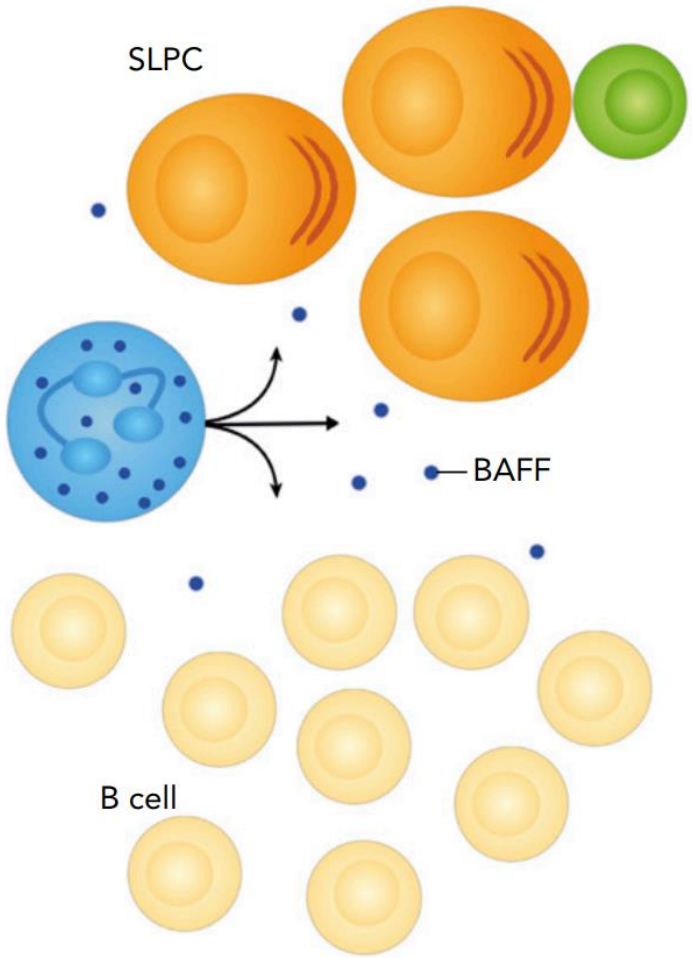
BAFF bestows longevity on splenic plasma cells

Julie Tellier | The Walter and Eliza Hall Institute; University of Melbourne

In this issue of *Blood*, Thai et al demonstrated that after B-cell depletion, elevated levels of unconsumed B-cell activating factor (BAFF) induced the emergence of long-lived plasma cells in the spleen.[1] Supported by neutrophils and CD4 T cells, this niche could be targeted by the administration of neutralizing antibodies against BAFF.

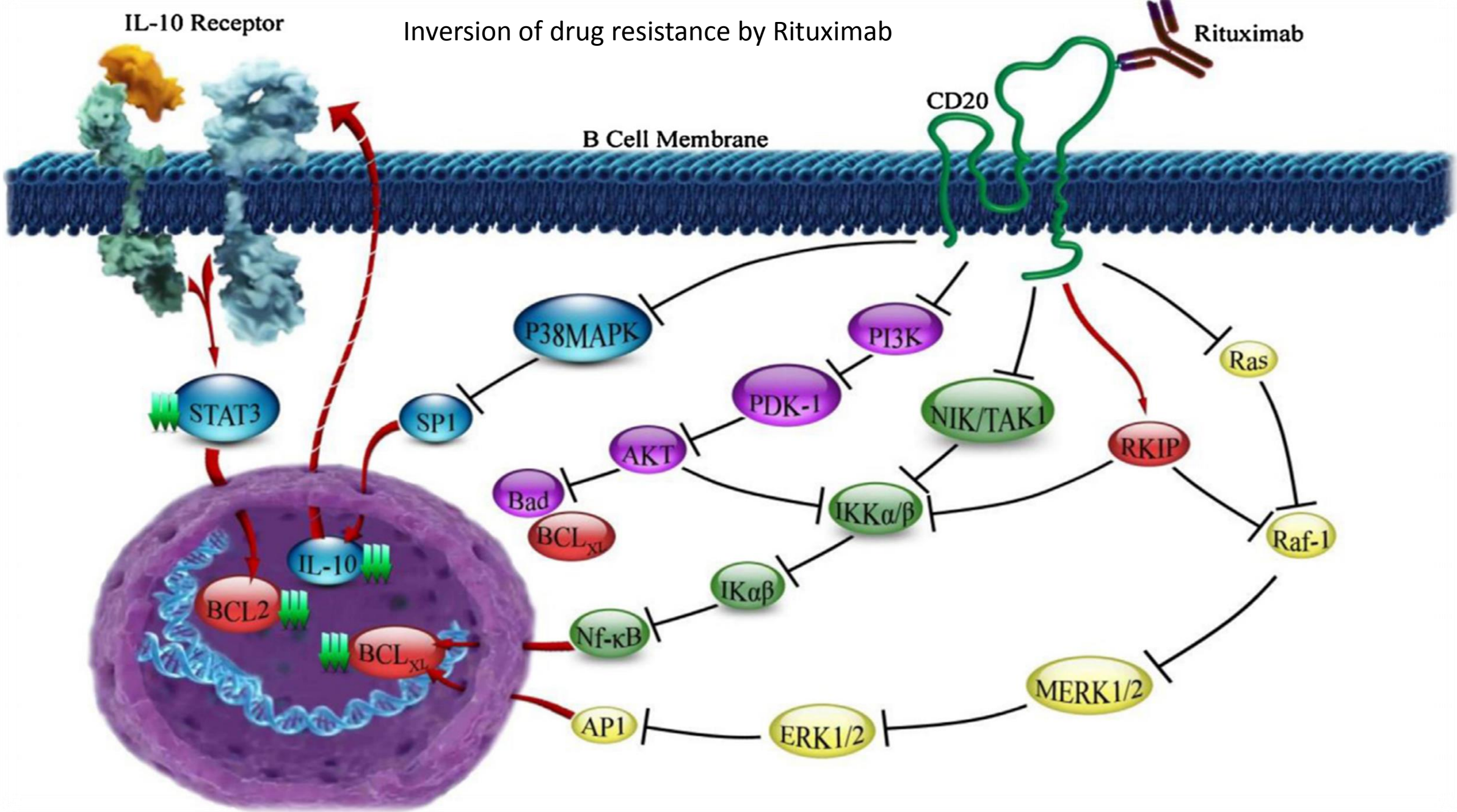
Blood ;2018 ,14:1500-1502

In the spleen, B cells consume most of the BAFF secreted by neutrophils. The antibody-secreted cell population is dominated by short-lived plasma cells (SLPCs).



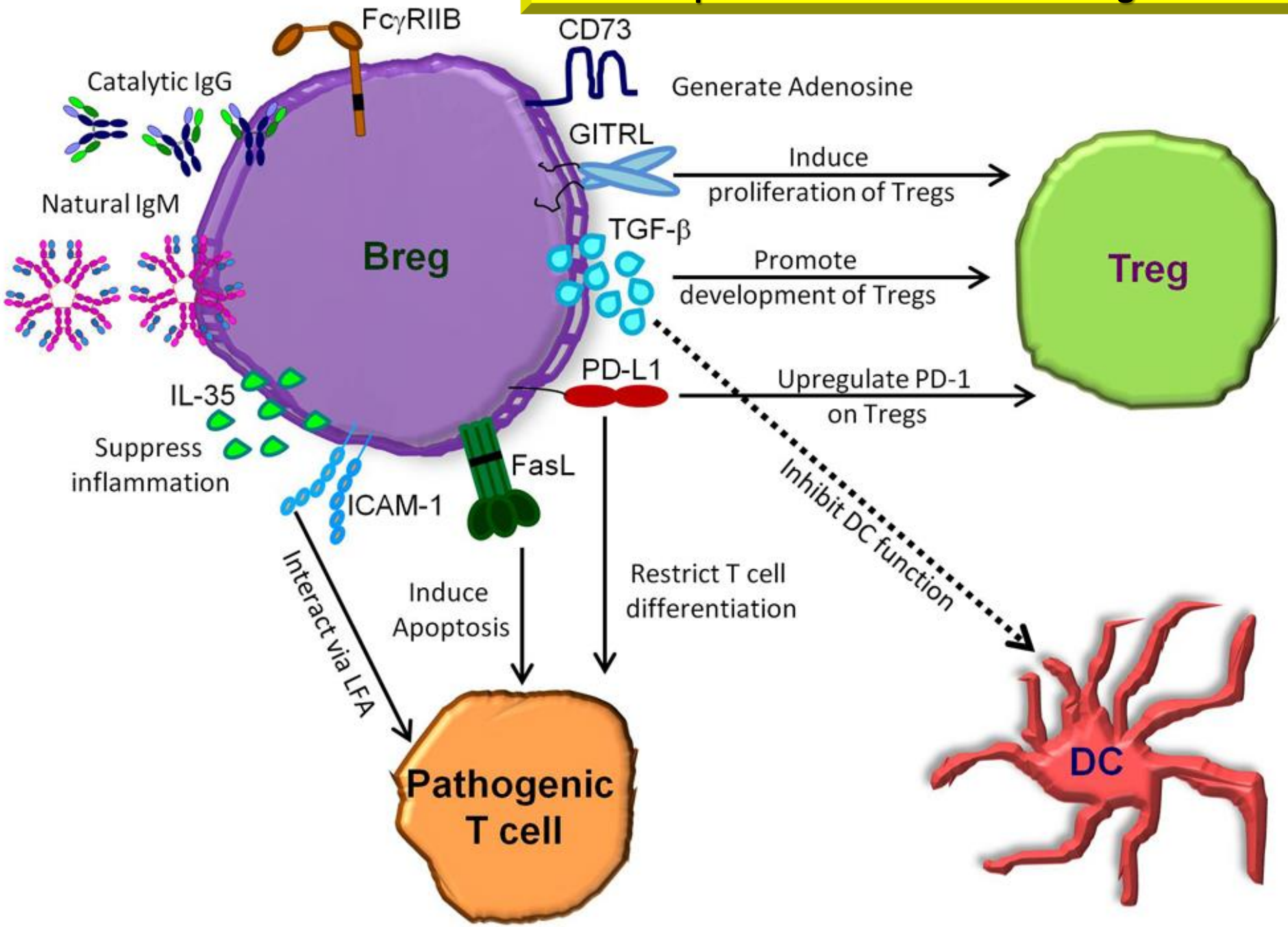
Blood ;2018 ,14:1500-1502

Inversion of drug resistance by Rituximab



N. Seyfizadeh et al. / Critical Reviews in Oncology/Hematology 97 (2016) 275–290

IL-10-independent mechanisms of Breg function

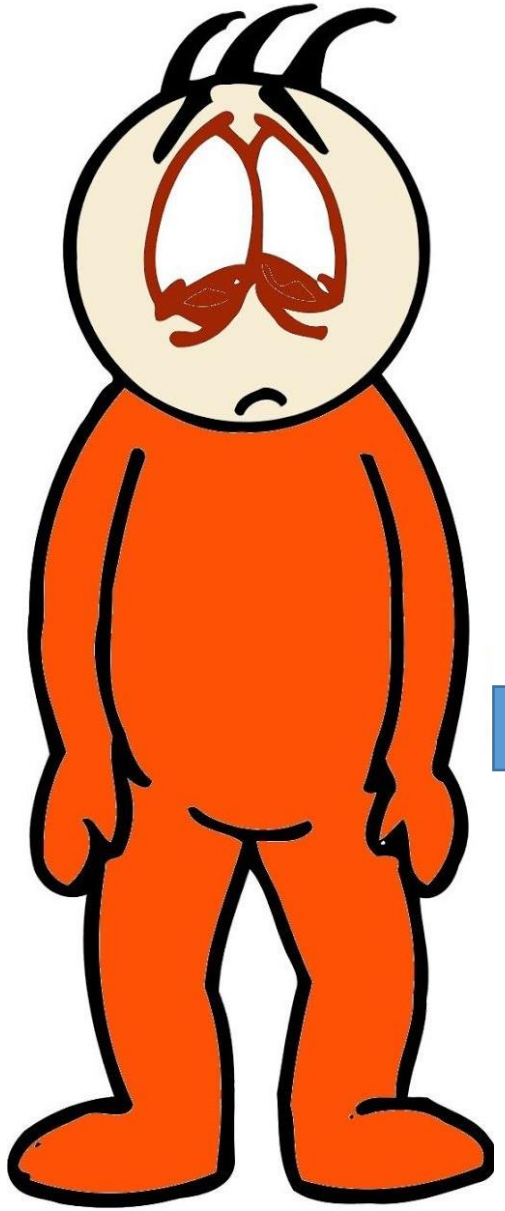


Differences in IL-10-producing B cells could explain the different response of B cells to Rituximab

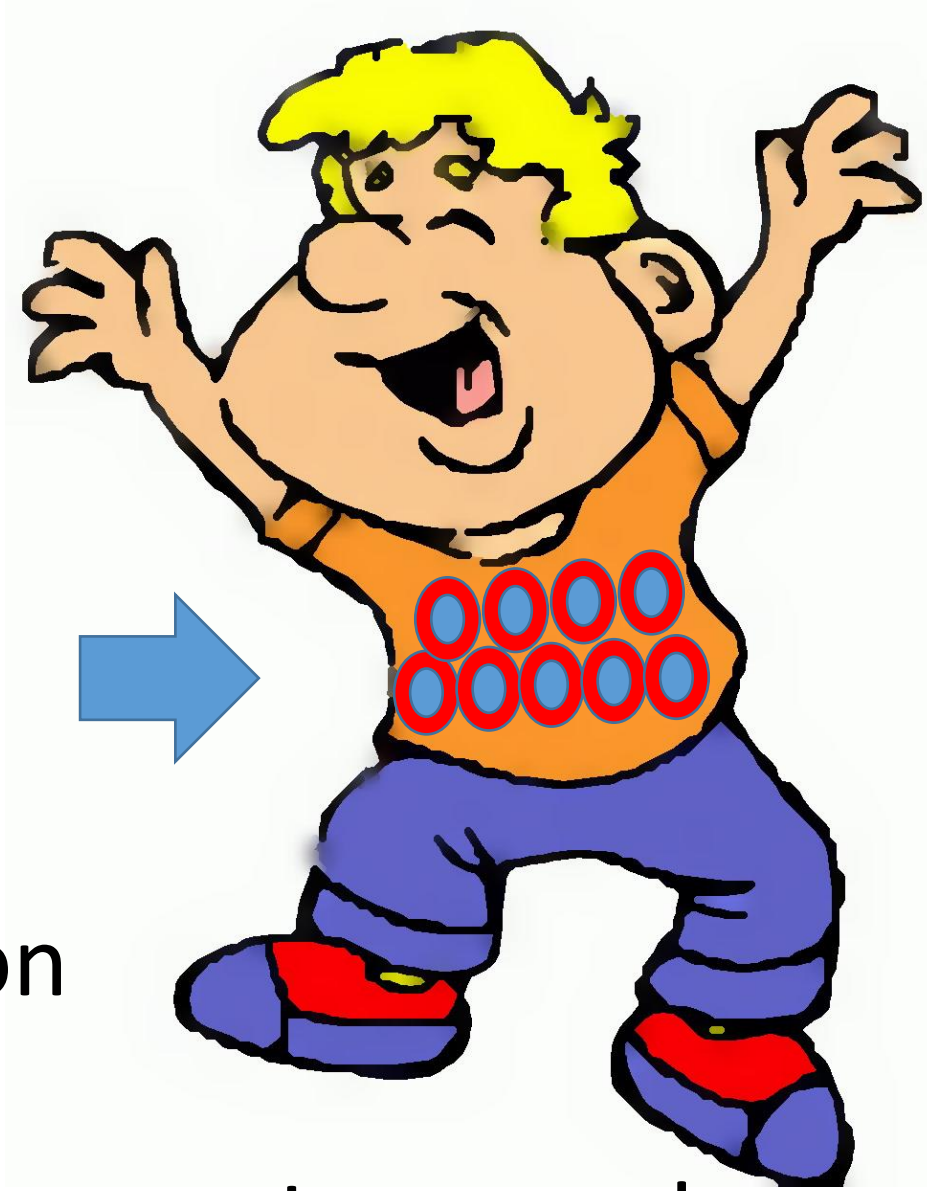
- “Good responder” to RTX in myasthenia gravis showed a rapid repopulation of CD19+ IL-10+ B cells after from 8 to 9 months compared with a “non-responder”.

- The depletion of anti-inflammatory B cells could contribute resistance to the Rituximab

Increased B10 cells



Helminthic infection



Patients with MS

Improved

IL-10+ B cells is a promising therapeutic goal for the treatment of autoimmune diseases. However, currently two unsolved problems hamper the development of a therapy based on IL-10+ B cells.

1)The methods used to generate IL-10+ B cells for therapeutic approaches are not suitable for a clinical setting.

2)The identity and phenotype of IL-10+ B cells remain uncertain

Table 1. Novel B cell therapies in glomerular disease

Agent	Mechanism of Action	Clinical Trials
Rituximab	Chimeric anti-CD20 mAb (B cell depletion)	SLE, ANCA (vasculitis), Wegener's, membranous, IgA, and FSGS
Ocrelizumab	Humanized anti-CD20 mAb with decreased immunogenicity and complement activation (B cell depletion)	SLE
Epratuzumab	Humanized anti-CD22 mAb (B cell depletion)	SLE
Belimumab	Humanized anti-BlyS mAb (inhibitor of B cell activation)	SLE
Atacicept	Fusion receptor protein (inhibitor of B cell activation)	SLE
Abatacept	Co-stimulation blockade (binds CD80/CD86 ligands)	SLE
Abetimus	Cross-links dsDNA on B cells	SLE

Clin J Am Soc Nephrol 5: 142–151, 2010

CONCLUSION

- The success of current B cell targeting therapies emphasizes the important roles B cells play in the pathogenesis of autoimmune diseases.
- B cells exhibit multiple powerful pro- and anti-inflammatory capacities.
- The current experience with B cell targeting therapies suggests that these findings also hold true in the clinic.
- Therapies that specifically deplete pathogenic B cells and plasma cells, or generate immunosuppressive B cells/plasma cells could hold great potential for the treatment of autoimmune diseases.
- In an optimal setting, the therapy would be tailored to the individual patient based on his/her predicted needs, benefits, and risks
- Pharmacogenomics should be considered as the personalized Medicine, “the therapy with the right drug at the right dose in the right patient”

Thank you for your attention