Failed B cell survival factor trials support the importance of memory B cells in multiple sclerosis.

David Baker[1], Gareth Pryce1, Louisa K. James[1], Klaus Schmierer[1,2,*], Gavin Giovannoni[1,2,*]

1. Blizard Institute, Queen Mary University of London, United Kingdom.

2. Clinical Board:Medicine [Neuroscience], Barts Health NHS Trust, London

* Joint senior authors

Running Title: Failed trials implicate memory B cells

Corresponding author: David Baker; Blizard Institute, Queen Mary University of London, 4 Newark Street, London E1 2AT. Tel:+442078822485; Fax:+442078822180; Email:david.baker@qmul.ac.uk

ABSTRACT

BACKGROUND: Clinical trials are probably the most informative experiments to help understanding of multiple sclerosis (MS) biology. Recent successes with CD20-depleting antibodies have focussed attention towards B cell subsets as important mediators in MS.

METHOD: We report and review the trial of tabalumab (NTC00882999), which inhibits B cell Activation Factor (BAFF), and contrast this with inhibition of A Proliferation-Inducing Ligand (APRIL) and BAFF using atacicept (NCT00642902).

RESULTS: Both tabalumab and atacicept induce depletion of mature B cells and inhibit antibody-formation, but they fail to deplete memory B cells and do not inhibit relapsing MS. Atacicept is reported to augment memory B cell responses and may precipitate relapse suggesting the importance of APRIL. However, BAFF inhibition can enhance peripheral blood memory B cell responses, which was not associated with augmented relapse.

CONCLUSIONS: Although other interpretations are possible, this data further supports the hypothesis that memory B cells may be of central importance in relapsing MS, as they are the major CD20+ B cell subset expressing APRIL receptors. It also suggests that quantitative and/or qualitative differences in B cell responses or other factors, such as immune-regulatory effects-associated with APRIL, may be important in determining whether MS reactivates following neutralization of peripheral B cell maturation and survival factors.

INTRODUCTION

Multiple sclerosis (MS) is the major immune-mediated demyelinating disease of the central nervous system (CNS). Although one can look to biology and animal models to understand the pathogenesis of MS, the most informative experiment is the human clinical trial. A successful trial or a negative result from a well-constructed study are informative. Although considered to be a T-cell mediated disease, response to therapy may suggest that B cell-selective agents exhibit control of relapsing MS [1]. It has been shown that CD20-B cell depleting agents control MS and inhibit lesion formation and clinical relapse [2]. Therefore, it is not surprising that targeting B cell survival factors was considered as an alternative approach to target autoimmunity [3-5]. As shown here, these have failed to inhibit MS, indicating that they are not adequately targeting the essential pathogenic disease mechanisms.

Positive clinical trials point towards memory B cells as important mediators in MS. Although attention has focused on the importance of T cells in MS pathogenesis, all agents that currently inhibit MS can limit entry of memory B cells into the CNS [1,6]. This hypothesis is potentially consistent with the aetiology, pathology and importantly the treatment response-hierarchy in MS [1,6]. As such, memory B cells could directly trigger pathology or may act indirectly, such as via activating pathogenic T cells [1,6]. Whilst CD20-specific therapy suggests a plasma cell-independent action, this could also involve direct actions on T cells, via depletion or alterations in T cell regulatory balance [1,6,7].

Negative clinical trials point towards memory B cells as important mediators in MS. To date there have been three MS-related trials of B cell-restricted survival factors relating to the tumour necrosis factor superfamily of ligands and B cell-restricted receptors (Figure 1) [3-5]. As reported and reviewed here, these fail to reduce memory B cells and have failed to control relapsing MS.

The tumour necrosis factor superfamily of B cell-related maturation and survival factors. B cell activating factor (BAFF/Tumour necrosis factor superfamily member 13B (TNFS13B/CD257)) promotes maturation and survival of B cells and is the dominant homeostatic regulator of peripheral B cell pools [8]. This binds and acts via the transmembrane activator, calcium modulator and cyclophilin ligand interactor (TACI/TNFSR13C/CD267) receptor, the BAFF-receptor (BAFF-R/TNFSR13B/CD268) and the B cell maturation antigen (BCMA/TNFSR17/CD269) (Figure 1) [8]. However, BAFF binds to the BAFF-R with significantly higher affinity than BCMA [8]. This latter receptor is also bound by a proliferation-inducing ligand (APRIL/ TNFSF13/CD256). APRIL acts on TACI, BCMA but, not BAFF-R and binds to BMCA with a higher affinity than BAFF (Figure 1) [8,9]. Both BAFF and APRIL are produced from membrane bound molecules by cleavage, which occurs in the Golgi with APRIL, to produce homotrimers and oligomers [8,9]. APRIL can also bind to heparin sulphate proteoglycans (HSPG) to create oligomerization, which serves to increase APRIL signalling [9]. Similarly, BAFF undergoes oligomerization to form 60mers that promotes the engagement of many receptors at a single site and is required for activation of TACI [10]. The biology is further complicated by the occurrence of alternative-splicing variants for the different receptors and the presence of soluble decoy receptors that can be shed following cleavage of the receptors [11]. These molecules mediate a variety of different functions within the B cell lineage and have been targeted to create a variety of therapeutic agents for autoimmunity and cancer [8,9].

Inhibition of soluble BAFF does not inhibit or augment multiple sclerosis. Tabalumab is a human IgG4 monoclonal antibody that neutralizes membrane and soluble BAFF [5,12] [NCT008829999]. This contrasts with belimumab that is a human IgG1 monoclonal antibody, licenced for the treatment of systemic lupus erythematosus, which targets soluble BAFF, notably the trimeric BAFF molecule [13]. Atacicept is a fusion protein of TACI and constant regions of human IgG1 that blocks BAFF and APRIL [3,4].

Whilst the data for the atacicept trial in MS (Table 1. NCT00642902. Treated with 0, 25, 75, 150mg atacicept within about a median of 6.9-8.6 years from first symptom) has been reported [3, 4], the data relating to the tabalumab trial (Table 1. Treated Q4W with 0, 4, 12, 40 or 120mg antibody from a median of 7.4-9.4 years after first symptom) has not been published. However, the conclusions and tabulated data (Table 1A) can be found in the public domain [5], [NCT0088299999]. Of the 245 people with MS randomised to tabalumab, 197 (80%) completed the study. The primary endpoint was the mean total cumulative number of gadolinium-enhancing (Gd+) magnetic resonance imaging lesions during the study. There were 1.521 and 1.758 lesions, averaged over weeks 12-24, in all-tabalumab and placebo groups, respectively, and the differences overall, or between any of the tabalumab groups and placebo, were not statistically significant [5]. Furthermore, there was no indication of any treatment influence on secondary outcomes. Notably there was no difference in the accumulation of T2 lesions or annualised relapse rate (Table 1A). Importantly, there was no evidence for enhanced numbers of relapses following tabalumab treatment (Table 1A). This contrasts with that reported following atacicept treatment [Table 1B], which led to the trial-termination [3,4].

Although the patient demographics between these two phase II trials are not identical (Table 1), they are similar and given that the apparent worsening was seemingly evident in the atacicept optic neuritis trial [4], could suggest that the tabalumab trial was sufficiently large to detect an enhanced relapse frequency. Indeed, relapse of MS was a reported adverse effect in the tabalumab report, so it is unlikely that an enhanced relapse-frequency was missed.

The adverse events of atacicept have been reported [3], as have those of tabalumab in trials not related to MS [12]. In MS, the proportion of people reporting at least one treatment-emergent adverse event, serious adverse event, and follow-up emergent adverse event was higher in the all-tabalumab group than placebo (68.1% (n=143) vs 48.6% (n=17), 11% (n=23) vs 5.7% (n=2), and 41.9% (n=88) vs 34.3% (n=12), respectively]; however, this was not dose-dependent [5]. Fatigue was the only consistent adverse event reported to occur in more than 5% of the groups (5.6%-11.4%) following tabalumab treatment compared to the placebo (0%). The data therefore suggests that tabalumab was inactive at the doses tested in MS. This would either suggest that the apparent worsening of MS following atacicept administration [3] was due to a combination of BAFF and APRIL inhibition or that blockade of APRIL was the major problem.

Expression profile of B cell-specific survival factors. Examination of BAFF and APRIL receptor gene expression within human B cell lineages indicate that BAFF-R is present on all peripheral B cell subtypes (Figure 2. Data extracted from the primary cell atlas [14] database. www.biogps.org). However, BAFF-R gene expression was low in CD34+ stem cells and pro and pre-B cells, which is

consistent with the reported levels of protein using flow cytometry [15,16]. Although BAFF-R was detected on plasma cells (Figure 2) consistent with the influence of belimumab of loss of peripheral plasma cells [13], in some instances, notably in the bone marrow BAFF-R can be lost from plasma cells [15]. This expression profile is consistent with the role of BAFF and BAFF-R as a positive regulator and survival factor for peripheral B cells [8]. The TACI receptor, based on relative gene levels, was most expressed on human memory B and plasma cells and at lower levels on other cell types (Figure 2), again consistent with protein expression, where it has been shown that TACI is upregulated during B cell activation [15,16]. BCMA message was expressed largely by plasma cells, again consistent with the reported expression of BCMA protein (Figure 2) [15,16]. These distributions may be different from that found in mice, notably related to the APRIL receptors, perhaps accounting for some species differences [8]. However, that human deficiency of TACI/TNFRSF13B can lead immunodeficiency, with a diminished memory B cell phenotype notably within the immunoglobulin (Ig) class-switched B cells, suggests the importance of this receptor to memory B cell biology [17].

Blockade of BAFF is associated with depletion of mature B cells and not memory B cells. Mutations in BAFF or the BAFF-R in mice cause B-cell lymphopenia and antibody deficiency [8,18]. Genetic deletion of human BAFF-R can lead to arrested B cell development at the transitional/immature to mature B cell stage, such that the numbers of all subsequent B-cell stages are severely reduced [18]. Following neutralization of BAFF, with tabalumab, there was a depletion of CD27-, IgD- cells, which were termed immature/transitional B cells by the sponsor (Figure 3). However, this must carry the proviso that in the absence of the flow cytometry methodology used in this study, the CD19+, CD27-, IgD- B cells may represent CD27- memory B cells [19, 20]. However, cells described as transitional B cells, detected using CD10, CD19, CD24, CD38, are depleted by tabalumab [21]. Long-lived plasma cells survival is likewise dependent on BAFF [22], consistent with the capacity of BAFF-inhibition to limit antibody production and reduce plasma cell numbers in humans [13,21]. However, depletion of naïve/mature B cells by tabalumab was the most evident feature on the analysis of B cell levels in MS [Figure 3]. Likewise, marked mature B cell depletion is a consistent effect following neutralization of BAFF with tabalumab [20] and belimumab [13] in other studies. This subset was also markedly (50-60%) depleted by atacicept in MS [3], consistent with that found elsewhere [23].

Although the data on memory B cell effects of atacicept in MS were not reported [3], it has been shown that atacicept induces a marked but transient increase in memory B cells, in the blood [23]. This has been suggested to be a possible reason for disease augmentation following atacicept treatment in MS [1]. This could be contrasted with some reports that the memory B cell response, notably the class-switched memory B cell response, is unaffected by neutralization of BAFF [13,24], as a possible reason for the disparity between BAFF and BAFF/APRIL inhibition. However, this now appears to be a too simplistic explanation. Although raw data was not available to perform statistics, blockade of BAFF by tabalumab induced a dose-dependent increase in memory B cells during treatment (Figure 3). This would be significant based on reported reference B cell subset levels [25]. Whilst many tabalumab studies have focussed on the mature and plasma cell depleting capacity [12, 21], augmentation of memory B cell responses within peripheral blood and lymphoid tissue has been reported [21]. Likewise, some studies with belimumab indicate a transient increase in memory B cells,

notably within the class-switched subset [13, 26]. This occurs rapidly following initiation of treatment and is then often followed by slow depletion over 52 weeks during treatment [24]. The unswitched memory B cell subset may decline to about -15% of baseline levels during 12-months of belimumab treatment and -52% of baseline levels at 18-months of treatment [13,26]. Whereas class-switched memory B cells appear not to be rapidly-depleted over 18 months of treatment and increase in some individuals [26]. This is perhaps consistent with the survival of class-switched memory B cells, despite the lack of BAFF [22]. However, with time and after several years of belimumab treatment it seems that even Ig class-switched memory B cells are depleted [26]. This suggests that mature B cell depletion eventually exhausts part of the downstream memory B cell [26]. Furthermore, it should not be surprising that peripheral blood B cell numbers may not predict treatment response, as relapsing autoimmunity can occur in people without a significant peripheral blood memory B cell pool, as shown following CD20-depletion therapy [6]. Whilst some of the enhanced memory B cell activity, seen here, could relate to anti-drug antibody responses, as they can and do occur with low frequency with these agents [12], in this MS study these were not detected against tabalumab (Table 1A). This suggests that other factors are important in the memory B cell responses. Indeed, as memory B cells are reported to be relatively insensitive to the survival activities of BAFF and APRIL [22,24], it suggests that other factors, such as loss of regulation may contribute to the increased memory cell numbers. This could be a central factor in the possible differences in response between tabalumab and atacicept. As such APRIL can exhibit negative regulatory activity that may be involved in the generation of regulatory B and T cells [27, 28]. Furthermore, it is known that TACI stimulation may regulate some of the activities of human B cells simulated via the BAFF-R [9]. Loss of regulatory activity may then allow disease breakthrough, in some individuals, but this requires further study.

Whilst we have focused on B cell-related effects, it is important to recognise that other activities of BAFF and APRIL inhibition, such as influences on plasmacytoid dendritic cells, astrocytes or even T cells, may account for the biological effects of treatment in MS [29-31]. Although APRIL targeting agents have been generated [9], they are unlikely to be investigated in MS following the problems recognised with atacicept. However, the data presented here further indicate the importance of reporting negative clinical studies.

The primary endpoint of both the tabalumab and atacicept indicated no treatment effect. Whilst this study attempts to dissect biological differences to explain variation between atacicept and tabalumab in terms of clinical effect, it should be kept in mind that both trials concluded that there were no treatment effects, based on their primary magnetic resonance imaging-based clinical outcomes [3,5]. The initial lesion loads appear to be similar between the studies reported here (Table 1). It is of interest therefore, that although the frequency of relapse is considered to be enhanced by atacicept [3], there appears to be little difference in the annualised relapse rate between atacicept and tabalumab treatment and the relapse rates found in the tabalumab trial and the placebo arm of the atacicept trial (Table 1). Furthermore, the frequency of conversion to MS in the optic neuritis (inflammation of the optic nerve that may be idiopathic of a sign of MS) trial of atacicept (Treated with 150mg atacicept within a median of about 0.2 years from onset) was not statistically different between drug (6/17 people [35.3%]) and placebo (3/17 people [17.6%]). Chi-squared with Yates correction P=0.4369) at the time the trial was terminated [4]. Therefore, both atacicept and tabalumab may

simply have been inactive at controlling relapsing MS. Never the less, if the idea about the central importance of memory B cells is correct, then a more focused approach to target these may be feasible and beneficial.

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LEGENDS

FIGURE 1. *BAFF/APRIL-related ligands and receptors for B cell control*. Potential binding activities and functions of BAFF and APRIL related molecules [13]. The positive effects of TACI may be mediated by APRILTACI/HSPG interactions and negative regulation may be via BAFF/TACI interactions.

FIGURE 2. *Gene expression of B cell growth factor receptors by B cell subsets*. Relative gene expression of BAFF-R (TNFRSF13C) probe set 1552892_at, TACI [TNFRSF13B] probe set 1423182_at and BCMA (TNFRSF17) probe 206641_at using Affymetrix Human Genome U133 Plus 2.0 expression arrays in the primary cell atlas at www.biogps.org [14]. The results represent the mean ± SD normalised arbitrary units of fluorescence intensity in the primary cell atlas [14]. The baseline was set at the level as the median expression [72.4, 82.4, and 12.4 respectively] of whole primary cell data set.

FIGURE 3. *The B cell depleting capacity of tabalumab treatment*. People with clinically-definite MS were treated with placebo or various doses of tabalumab administered every 4 weeks (Q4W) for 24 weeks. Peripheral blood was collected and stained to detect (CD19+, CD27+,IgD-) cells termed transitional/immature cells by the sponsor, although they may represent double negative memory cells if no additional markers were used in their detection[19,21], mature (CD19+,CD27-,IgD+), unswitched memory (CD19+,CD27+,IgD+) or class-switched memory (CD19+,CD27+,IgD-) B cells and the mean ± standard error of the mean change in cell number (cells/µl) was reported. Data were extracted from www.clinicaltrials.gov (NCT00882999). Baseline values were not reported but reference median B cell number for 26-50 year olds is about: 4 immature/transitional (CD24+,CD38+) B cells cells/µl, 131 mature (CD27,IgD+) B cells/µl, 35 Ig non-switched (CD27+,IgD+)/µl memory B cells, 29 Ig class-switched (CD27+,IgD-) memory B cells/µl and 7 double-negative (CD27-,IgD-) memory B cells/µl [25].

Table 1. *Demographics and treatment outcomes in phase II tabalumab and atacicept trials in MS*

Table 1A	Dose of tabalumab				
Tabalumab NCT00882999 trial	Placebo	4mg	12mg	40mg	120mg
Number	35	35	34	34	36
Age (Year)	40.3 ± 12.0	41.7 ± 10.2	43.1 ± 10.1	40.8 ± 10.8	40.8 ± 11.1
Sex (% Female)	68.6%	68.6%	64.7%	79.4%	58.3%
Time from first symptom (years)	7.4 ± 6.70	8.5 ± 7.81	9.4 ± 6.96	9.2 ± 7.49	8.9 ± 9.52
Mean Relapses past year	1.5 ± 1.38	1.4 ± 1.26	1.3 ± 0.51	1.4 ± 0.73	1.2 ± 0.56
Baseline No. T1 Gd+ lesions	1.2 ± 2.08	1.1 ± 2.64	0.5 ± 0.93	1.1 ± 1.91	1.4 ± 2.60
Volume T2 lesions (mL)	7.0 ± 8.07	8.5 ± 10.53	7.8 ± 9.21	6.6 ± 7.92	9.0 ± 11.90
No. T1 Gd+ lesion per scan	1.76 ± 3.62	1.82 ± 3.31	0.71 ± 1.10	1.24 ± 2.00	1.48 ± 2.83
No. New T2 lesions at 24 week	1.3 ± 2.79	1.0 ± 2.37	0.7 ± 1.51	1.2 ± 2.42	1.7 ± 4.28
No New T2 lesions at 48 week	1.5 ± 4.06	1.3 ± 0.65	0.4 ± 0.65	1.8 ± 6.04	2.8 ± 6.04
EDSS at week 24	2.77 ± 1.42	2.91 ± 0.99	2.78 ± 1.33	2.62 ± 1.25	2.17 ± 1.43
EDSS at week 48	2.60 ± 1.38	2.96 ± 1.26	2.46 ± 1.61	2.74 ± 1.07	2.18 ± 1.57
Relapse-free Week 24 in trial	83.9%	72.4%	82.8%	77.4%	84.8%
Relapse-free week 48	72.4%	70.4%	73.1%	64.5%	75.0%
Annualised relapse rate week 24	0.71± 2.84	0.75± 1.57	0.80± 1.83	0.33± 0.79	0.38± 0.87
Annualised relapse rate week 48	0.66± 2.81	0.67± 1.46	0.64± 1.28	0.36± 0.65	0.24± 0.46
MSFC week 24	0.24 ± 0.61	0.05 ± 0.74	0.11 ± 0.46	0.02 ± 0.37	0.17 ± 0.54
Anti-drug antibodies week 0-108	0%	0%	0%	0%	0%
Serious Adverse events	2.86%	5.71%	11.76%	5.88%	8.33%
Other adverse events	48.57%	60.00%	64.71%	73.53%	77.78%

Table 1B	Dose of atacicept			
Atacicept NCT00642902 trial	Placebo	25mg	75mg	150mg
Number	63	63	64	65
Age (Year)	37.7± 10.5	37.5 ± 8.5	38.0 ± 10.1	37.7 ± 10.5
Sex (% Female)	71.4%	54.0%	68.8%	70.8%
Time from First attack (Years)	7.5 ± 7.5	8.6 ± 7.0	7.9 ± 7.2	6.9 ± 6.8
Mean Relapses past year	N.R.	N.R.	N.R.	N.R.
Baseline No. T1 Gd+ lesions	2.2 ± 4.1	1.1 ± 2.1	1.4 ± 3.7	1.5 ± 4.7
Volume T2 lesions (mm^3)	7531 ± 9813	5574 ± 8451	7537 ± 11297	6092 ± 0326
EDSS baseline	2.49 ± 1.19	2.83 ± 1.31	2.62 ± 1.27	2.54 ± 1.28
T1 Gd+ lesion per scan [95% CI]	3.07 [1.40-6.77]	2.26 [0.09-5.27]	2.30 [1.08-4.92]	2.49 [1.18-5.27]
Lesions/participant Week 24	0.83 ± 1.70	1.50 ± 2.79	1.54 ±2.96	1.54 ± 2.94
Lesion/participant Week 36	0.43 ± 0.90	1.68 ± 2.7	1.38 ±1.93	1.54 ± 2.94
Relapses in blinded trial	12	24	24	31
Relapse Free in trial	81.0%	69.8%	71.9%	61.5%
Annualised relapse rate [95% CI]	0.38 [0.17-0.87]	0.86 [0.43-1.74]	0.79 [0.40-1.58]	0.98 [0.52-1.81]

CI confidence interval, EDSS expanded disability status scale, Gd+ Gadolinium-enhancing, MSFC multiple sclerosis functional composite score
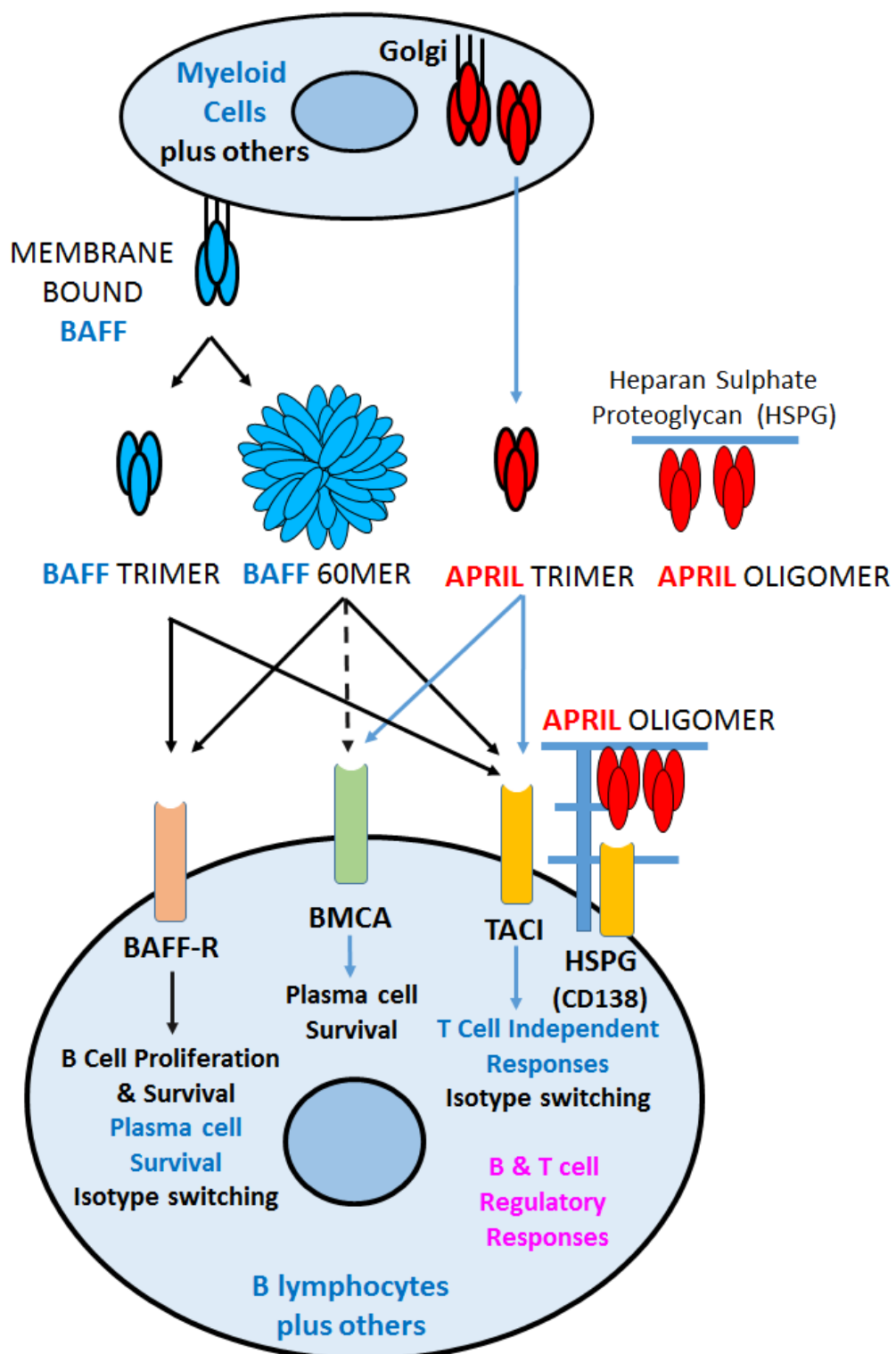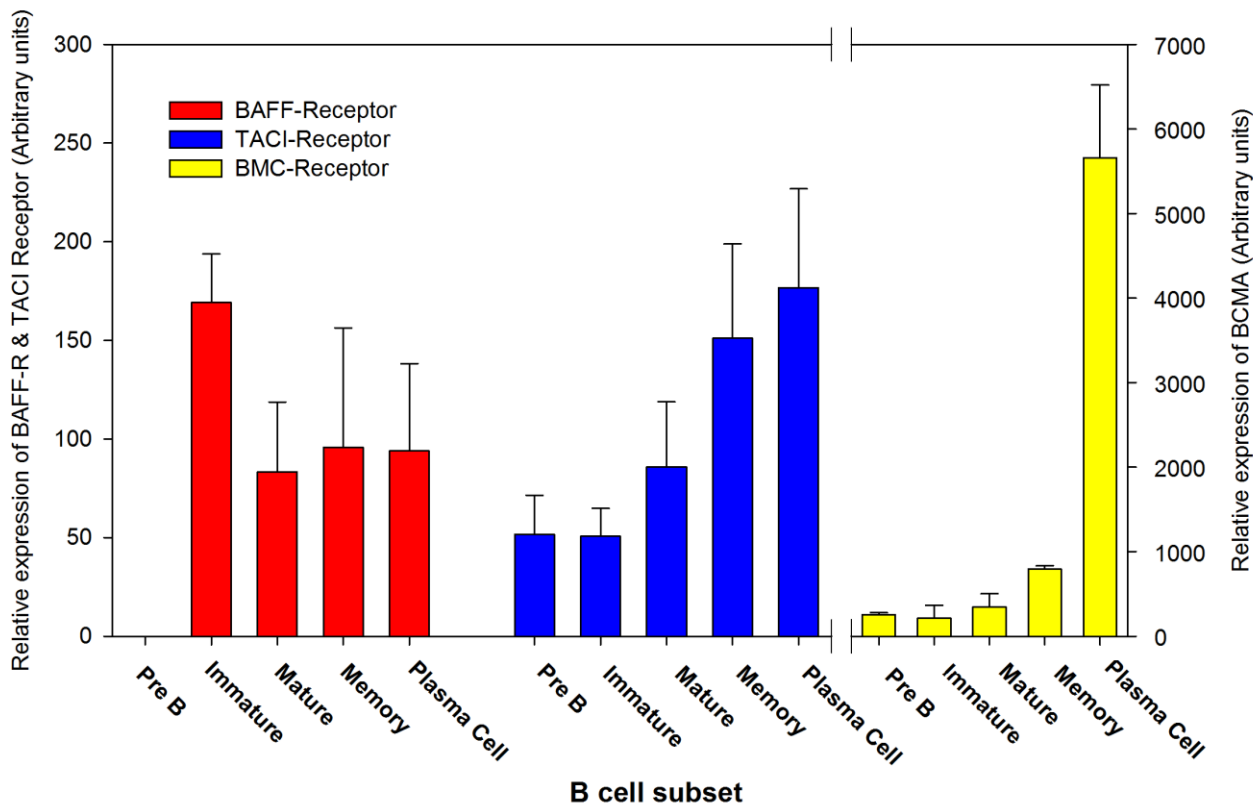
FIGURE 1

FIGURE 2

FIGURE 3