

## Targeting Myddosome Assembly in Waldenstrom Macroglobulinaemia

*MYD88* mutations are expressed in Waldenstrom Macroglobulinaemia (WM) (95–97%), immune-privileged lymphomas (50–80%), activated B-cell (ABC) subtype of diffuse large B-cell lymphoma (DLBCL) (15–30%), marginal zone lymphoma (6–10%) and chronic lymphocytic leukaemia (CLL) (3–8%) (Montesinos-Rongeri *et al*, 2011; Ngo *et al*, 2011; Pasqualucci *et al*, 2011; Puente *et al*, 2011; Treon *et al*, 2012; Martínez *et al*, 2014). In WM, nearly all cases express the *MYD88*<sup>L265P</sup> mutation (Treon *et al*, 2012); 50–80% of IgM MGUS patients express *MYD88*<sup>L265P</sup> by allele-specific polymerase chain reaction, and its expression is associated with an increased risk of malignant progression (Varettoni *et al*, 2013; Xu *et al*, 2013).

The importance of mutated *MYD88* in supporting tumour cell survival in ABC DLBCL and WM was established by *MYD88* gene knock-down and/or over-expression studies (Ngo *et al*, 2011; Treon *et al*, 2012; Yang *et al*, 2013). *MYD88* dimerization is necessary for assembly of the Myddosome, a structure composed of *MYD88* dimers that recruit and activate interleukin-1 receptor-associated kinase (IRAK) 4, which in turn recruits and activates IRAK1 or 2. The *MYD88*:IRAK4:IRAK1/2 complex can then trigger canonical nuclear factor- $\kappa$ B (NF $\kappa$ B) growth and survival signalling (Ngo *et al*, 2011; Yang *et al*, 2013). The Myddosome can also activate Bruton Tyrosine Kinase (BTK), which can promote canonical NF $\kappa$ B signalling in mutated *MYD88* WM cells (Yang *et al*, 2013).

The *MYD88* protein is composed of an N-terminal death domain (DD) spanning amino acids 40–119, an intermediate linker domain (ID) that spans amino acids 120–173, and a C-terminal Toll/IL1 receptor (TIR) domain that encompasses amino acids 174–309 (NCBI NP\_002459.2). Upon ligand binding to TLR/IL1R, the TIR domain facilitates binding to the receptor complex, and promotes *MYD88* dimerization. Loiarro *et al* (2013) used site-directed mutagenesis of conserved residues within the *MYD88* TIR domain to analyse their impact on *MYD88* protein signalling. Their work revealed that mutation of Glu<sup>196</sup>, Ser<sup>257</sup> and Arg<sup>301</sup> [per National Center for Biotechnology Information (NCBI)NP\_002459.2 annotation] interfered with TIR-mediated *MYD88* dimerization, IRAK recruitment, and reduced NF $\kappa$ B activation. The over-expression of two *MyD88* (*MYD88*<sup>164–202</sup> and *MYD88*<sup>181–202</sup>) mini-peptides that included Glu<sup>196</sup> in wild-type *MYD88* (*MYD88*<sup>WT</sup>) THP-1 human monocyte cells also blocked TLR/IL1R triggered *MYD88* dimerization and NF $\kappa$ B activation.

There is evidence that the *MYD88* DD domain can also facilitate *MYD88* dimerization and *MYD88*:IRAK4 heterodimerization. Structural modelling has highlighted Ser<sup>47</sup> and Arg<sup>111</sup> (per NCBI NP\_002459.2 annotation) as contributors to Myddosome assembly, IRAK4 recruitment and NF $\kappa$ B signalling, though without an intact TIR domain such interactions appear weak (George *et al*, 2011). The understanding of how *MYD88* and IRAK4 DD domains interact to support Myddosome assembly has been aided by crystal structure modelling of the *MYD88*:IRAK4:IRAK2 DD complex that shows Val<sup>56</sup>, Ala<sup>57</sup>, Glu<sup>65</sup>, Tyr<sup>71</sup>, Ile<sup>74</sup> and Arg<sup>75</sup> (per NCBI NP\_002459.2 annotation) of *MYD88* as critical determinants of *MYD88*:IRAK4 binding (Lin *et al*, 2010).

In contrast to native *MYD88*, mutated *MYD88* protein can assemble without external stimuli, and trigger constitutive NF $\kappa$ B activation (Ngo *et al*, 2011; Treon *et al*, 2012; Yang *et al*, 2013). All activating *MYD88* mutations observed in B-cell malignancies, including *MYD88*<sup>L265P</sup>, reside in the TIR domain. Relative to *MYD88*<sup>WT</sup>, mutated *MYD88* protein shows enhanced IRAK4 and IRAK1 binding, and NF $\kappa$ B activation. While the precise structural interaction(s) that promote constitutive *MYD88* homodimeric and IRAK heterodimeric interactions remain to be clarified in *MYD88* mutated cells, the potential to block Myddosome self-assembly may be clinically relevant. We therefore sought to disrupt Myddosome signalling by systematic evaluation of mini-peptides designed to compete with *MYD88* TIR and DD domain interactions, and studied their impact on downstream signalling and survival in *MYD88* mutated WM cells.

Oligonucleotides corresponding to the TIR and DD domain peptide sequences (Fig 1A) were cloned into Lenti-X<sup>TM</sup> Tet-One<sup>TM</sup> (Clontech Laboratories, Inc., Mountain View, CA, USA) inducible vector with an N-terminal GFP fusion sequence: *MYD88* TIR domain: P<sub>181–202</sub> (sense: CTATTGCCCCAGCGACATCCAGTTT, anti-sense: CAGTCGATAGTTGTCTGTTCCAGTTGC), P<sub>256–292</sub> (sense: CTCTCTCCAGGTGCCCATCAGAA, anti-sense: AGGGTTGGTGTAGTCGCAGACAGT), P<sub>190–197</sub> (oligonucleotide: GAGATGATCCGGCAACTGGAACAG), P<sub>191–198</sub> (oligonucleotide: ATGATCCGGCAACTGGAACAGACA), P<sub>195–202</sub> (oligonucleotide: CTGGAA-CAGACAAACTATCGACTG), P<sub>295–302</sub> (oligonucleotide: AAATCTTGGTTCTGGACTCGCCTT), and *MYD88* DD domain: P<sub>40–85</sub> (sense: CGGCGCCGCCTGTCTCTGTT, anti-sense: GC CAGTGGGGTCCGCTTGT). Molecular modelling depicting the surface areas and ribbon structures of the *MYD88* TIR

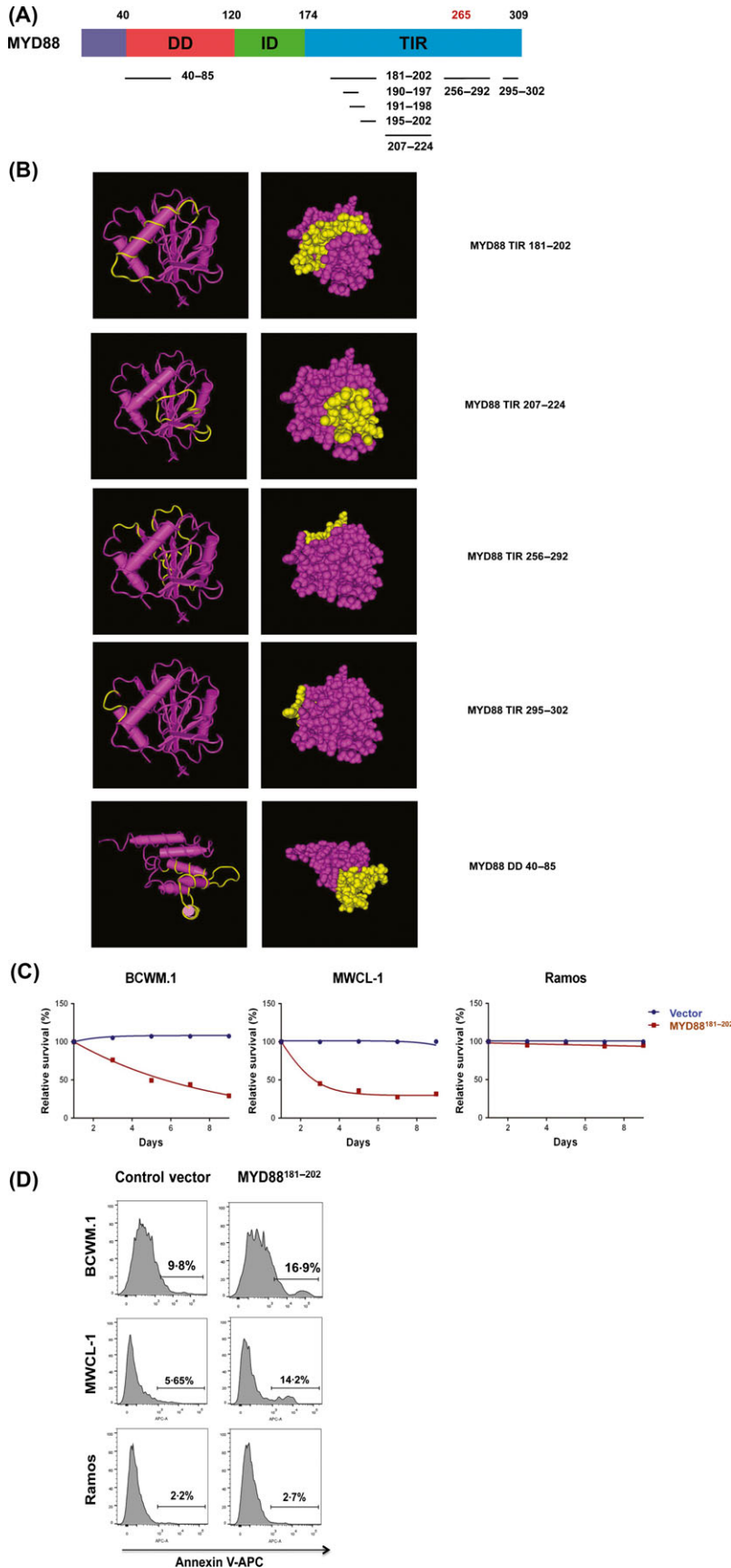
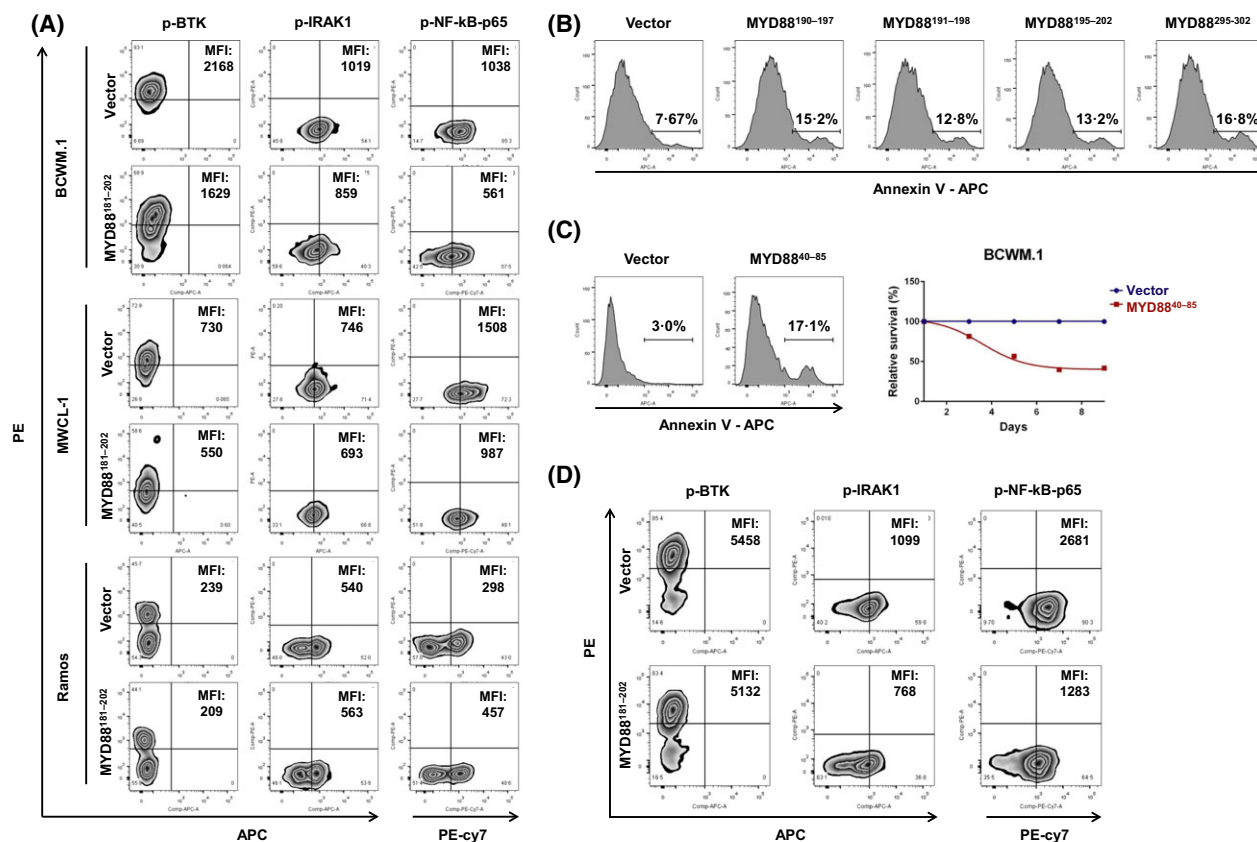


Fig 1. MYD88 TIR domain dimerization supports pro-survival signalling in MYD88 mutated cells. (A) Structure of MYD88 protein identifying death domain (DD), intermediate domain (ID) and Toll/IL-1 receptor (TIR) domain, and regions targeted for interference by mini-peptide constructs based on NCBI MMDB 108985 (TIR) MMDB:82515 (DD) crystal structure models. (B) Molecular modelling depicting surface areas and ribbon structures of the MYD88 protein TIR and DD domain regions that were targeted for interference by mini-peptide constructs. (C) Results of AlamarBlue<sup>®</sup> growth assays following transduction of MYD88 mutated BCWM.1 and MWCL-1 or MYD88 wild-type Ramos cells with control vector or vector coding for MYD88<sup>181-202</sup> mini-peptides. (D) Apoptotic changes following 72 h of doxycycline induction by Annexin V staining on GFP<sup>+</sup> BCWM.1, MWCL-1 and Ramos cells transduced with control vector or vector coding for MYD88<sup>181-202</sup> mini-peptides. Representative results from two independent experiments are shown.



**Fig 2.** Impact of TIR and DD Domain Mini-Peptides on Pro-Survival Signalling in *MYD88* mutated WM cells. (A) PhosFlow studies to assess changes in pBTK<sup>Y223</sup>, pIRAK1<sup>T209</sup> and pNFκB-p65<sup>S529</sup> activation following 24 h of doxycycline induction for GFP<sup>+</sup> BCWM.1, MWCL-1 and Ramos cells following transduction with a control vector or vector coding for *MYD88*<sup>181-202</sup> mini-peptide. (B) Apoptotic changes following 72 h of doxycycline induction by Annexin V staining on GFP<sup>+</sup> BCWM.1 cells transduced with control vector or vector coding for 8-mer *MYD88* mini-peptides that target Glu<sup>196</sup> and Arg<sup>301</sup>. (C) Results of apoptosis assay following 72 h of doxycycline induction, and AlamarBlue<sup>®</sup> growth assays following transduction of BCWM.1 cells with control vector or vector coding for a mini-peptide that targets the DD domain (*MYD88*<sup>40-85</sup>). (D) PhosFlow studies to assess changes in pBTK<sup>Y223</sup>, pIRAK1<sup>T209</sup> and pNFκB-p65<sup>S529</sup> activation following 24 h for GFP<sup>+</sup> BCWM.1 cells following transduction with a control vector or vector coding for a DD domain (*MYD88*<sup>40-85</sup>) mini-peptide. Representative results from two independent experiments are shown.

and DD domain regions targeted for interference by mini-peptide constructs based on NCBI MMDB 108985 (TIR) MMDB:82515 (DD) crystal structure models are shown in Fig 1B. Following lentiviral infection and puromycin selection in tetracycline-free media, *MYD88*<sup>L265P</sup> mutated BCWM.1 and MWCL-1 or *MYD88*<sup>WT</sup> Ramos cells were treated with doxycycline. Cell survival was then assessed on sorted GFP<sup>+</sup> cells with AlamarBlue<sup>®</sup> (Invitrogen, Carlsbad, CA, USA). Annexin V staining (BD Biosciences, San Jose, CA, USA) was used for detecting apoptotic changes on GFP<sup>+</sup> cells by flow cytometry. To detect changes in *MYD88* downstream signalling, PhosFlow<sup>®</sup> analysis was performed for pBTK<sup>Y223</sup>, pNFκB-p65<sup>S529</sup> (BD Biosciences) and pIRAK1<sup>T209</sup> (Abcam, Cambridge, MA, USA) on GFP<sup>+</sup> cells (Yang *et al*, 2013).

Given that mini-peptides expressing Glu<sup>196</sup> within the TIR domain blocked TLR/IL1R-triggered *MYD88* dimerization and NFκB activation in *MYD88*<sup>WT</sup> THP-1 human monocytes,

we first examined a mini-peptide (*MYD88*<sup>181-202</sup>) that targeted this region in *MYD88*<sup>L265P</sup> mutated BCWM.1 and MWCL-1 cells, and *MYD88*<sup>WT</sup> Ramos cells (Figs 1A,B).

Expression of *MYD88*<sup>181-202</sup> blocked growth of BCWM.1 and MWCL-1 cells, but did not impact growth of *MYD88*<sup>WT</sup> Ramos cells (Fig 1C). Annexin V staining showed apoptotic changes in *MYD88*<sup>L265P</sup> but not *MYD88*<sup>WT</sup> cells transduced with *MYD88*<sup>181-202</sup> (Fig 1D). Moreover, pro-survival signalling (pBTK<sup>Y223</sup>, pIRAK1<sup>T209</sup>, pNFκB-p65<sup>S529</sup>) was abrogated in *MYD88*<sup>L265P</sup> but not *MYD88*<sup>WT</sup> cells transduced with *MYD88*<sup>181-202</sup> (Fig 2A). Expression of smaller mini-peptides (8-mers) that overlapped Glu<sup>196</sup> (*MYD88*<sup>190-197</sup>, *MYD88*<sup>191-198</sup> and *MYD88*<sup>195-202</sup>) also showed increased apoptosis at 72 h in *MYD88*<sup>L265P</sup> mutated BCWM.1 cells (Fig 2B). In contrast, no sustained growth inhibition of BCWM.1 cells with any of the 8-mer peptides was observed (data not shown). In addition to Glu<sup>196</sup>, Loiarro *et al* (2013) also showed that mutation of Ser<sup>257</sup> and Arg<sup>301</sup> in *MYD88*

also interfered with TIR-mediated dimerization. To clarify their contribution to MYD88-directed survival signalling, BCWM.1 cells were also transduced with vectors coding for mini-peptides spanning amino acids 256–292 and 295–302. Apoptotic changes relative to control vector were observed in only MYD88<sup>295-302</sup> transduced BCWM.1 cells (Fig 2B). Neither MYD88<sup>256-292</sup> nor MYD88<sup>295-302</sup> impacted pBTK<sup>Y223</sup>, pIRAK1<sup>T209</sup> or BCWM.1 cell survival, while moderate reductions in pNFκB-p65<sup>S529</sup> were observed with only MYD88<sup>256-292</sup> (data not shown). Transduction of a mini-peptide interfering with BB-loop interactions (MYD88<sup>207-224</sup>) also showed weak or no reduction in pro-survival signalling (pBTK<sup>Y223</sup>, pIRAK1<sup>T209</sup>, pNFκB-p65<sup>S529</sup>), nor were any meaningful apoptotic or sustained growth inhibitory effects observed relative to control vector transduced BCWM.1 cells (data not shown). The findings with MYD88<sup>256-292</sup> and MYD88<sup>207-224</sup> were particularly instructive, given that most of the described activating MYD88 mutations are located in either the BB loop, or at position 265.

Further to these experiments, we also sought to clarify the contributions of the DD domain to pro-survival signalling in MYD88<sup>L265P</sup> mutated WM cells. We therefore transduced BCWM.1 cells with either a control vector or vector coding for a mini-peptide that spanned amino acids 40–85 (MYD88<sup>40-85</sup>) within the DD domain of MYD88. Expression of the MYD88<sup>40-85</sup> mini-peptide in BCWM.1 cells was associated with increased apoptosis, and contributed to sustained growth inhibition (Fig 2C), as well as reduced pIRAK1<sup>T209</sup> and pNFκB-p65<sup>S529</sup> activation (Fig 2D).

The findings therefore suggest that optimal survival signalling of MYD88 mutated WM cells involves TIR domain residues overlapping Glu<sup>196</sup>, and possibly residues extending from amino acids 40–85 in the DD domain. Reductions in IRAK and/or BTK signalling probably contributed to decreased WM cell survival, though greater reductions in pNFκB-p65<sup>S529</sup> were observed in comparison to pIRAK or pBTK following transduction of MYD88<sup>181-202</sup> or MYD88<sup>40-85</sup>. These findings may indicate either a critical scaffold function for the IRAK and/or BTK proteins beyond their well-established pro-survival kinase activity, and/or the presence of other binding partners that support growth signalling in MYD88 mutated WM cells. A scaffold function for TLR/IL1R triggered IRAK1 activity has been previously described in MYD88<sup>WT</sup> cells (Böl *et al*, 2005). A potential scaffold function for the IRAK proteins may also explain why knockdown of IRAK1 or IRAK4 produces higher levels of apoptosis than observed with inhibitors targeting these kinases in MYD88 mutated WM cells (Yang *et al*, 2013, 2015) Lastly, the findings also provide regions of interest that are conducive to the development of small molecules, peptidomimetics or stapled peptides for potential therapeutic application. Larger peptide sequences (>8-mers) may be needed within the TIR MYD88<sup>181-202</sup> domain to achieve sustained growth suppression as observed in our studies. The development of stapled peptides may be particularly suitable, as longer (20-mer peptides) have been developed for therapeutic

application by this approach (Walensky & Bird, 2014). In addition, the MYD88<sup>181-202</sup> domain has an alpha helical configuration that is ideal for manufacturing stapled peptides (Fig 1B). It is also possible that multiple stapled peptides targeting both the TIR and DD domains could be used to more optimally block Myddosome assembly. In summary, we show that interference of Myddosome assembly within select regions of the TIR and DD domains can impact growth and survival signalling of MYD88<sup>L265P</sup> mutated WM cells. Our findings provide a framework for developing agents that interfere with Myddosome assembly in WM, and possibly for other lymphoproliferative disorders driven by MYD88-activating mutations.

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## Author contributions

XL, GY, and SPT designed the study. GY and XL designed the primers. XL, JGC performed the lentiviral transduction experiments. JC, NT, and GY performed the signalling studies. CJP and JJC provided samples. ZRH, SB, NG, and ST performed data analysis.

## Conflict of interest disclosures

The co-authors have no relevant disclosures for this work.

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