

# Disruption of the mTOR-eIF4F Axis by Selectively Targeting PI3K $\delta$ and Proteasome Potently Inhibits Cap Dependent Translation of c-Myc in Aggressive Lymphomas

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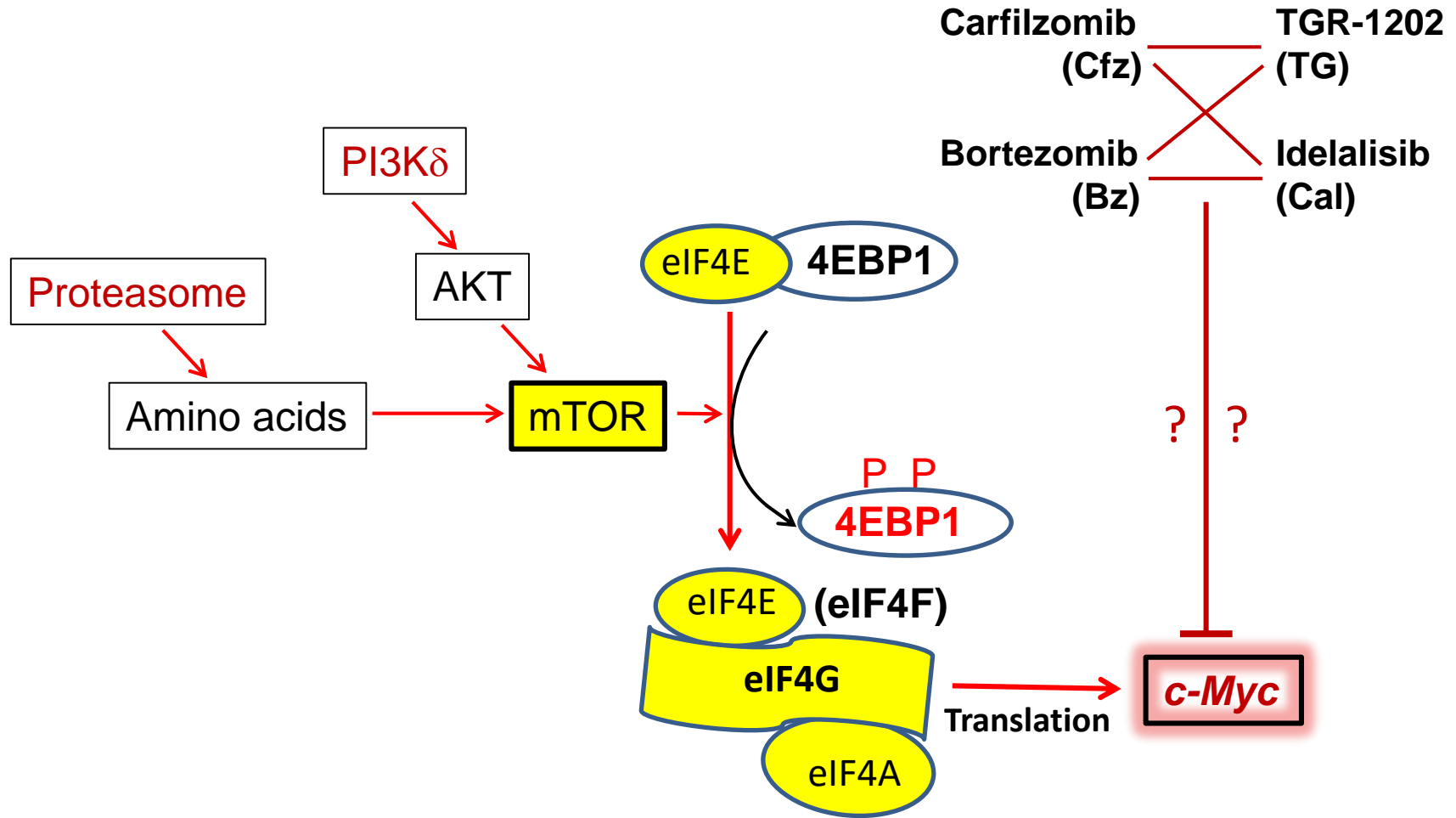


**NewYork-Presbyterian**  
The University Hospital of Columbia and Cornell

# Therapeutic Strategy Targeting c-Myc in Cancer Is Urgently Needed

- C-MYC rearrangement is a risk factor for poor survival in diffuse large B cell lymphoma (DLBCL)  
Savage et al. Blood 2009; Barrans et al. JCO 2010; Copie-Bergman et al. Blood 2015
- C-MYC expression is a risk factor for poor survival in DLBCL  
Green TM et al., J Clin Oncol. 2012; Johnson NA, et al., J Clin Oncol. 2012; Hu S et al., Blood. 2013
- ***However, no drugs specifically targeting the activity of c-Myc have been approved for any cancer.***
- C-Myc is a master transcription factor, and lacks enzymatic activity
- Structurally, c-Myc lacks globular functional domains for small molecule targeting
- The extended interaction between the c-Myc and Max offers no apparent site for positioning a small-molecule inhibitor.
- Targeting the BET bromodomains is a promising strategy for c-Myc driven cancer  
McKeown and Bradner, CSH Perspective 2014

# Potential Strategies to Silence the Translation of c-Myc through Targeting the mTOR-eIF4F Axis

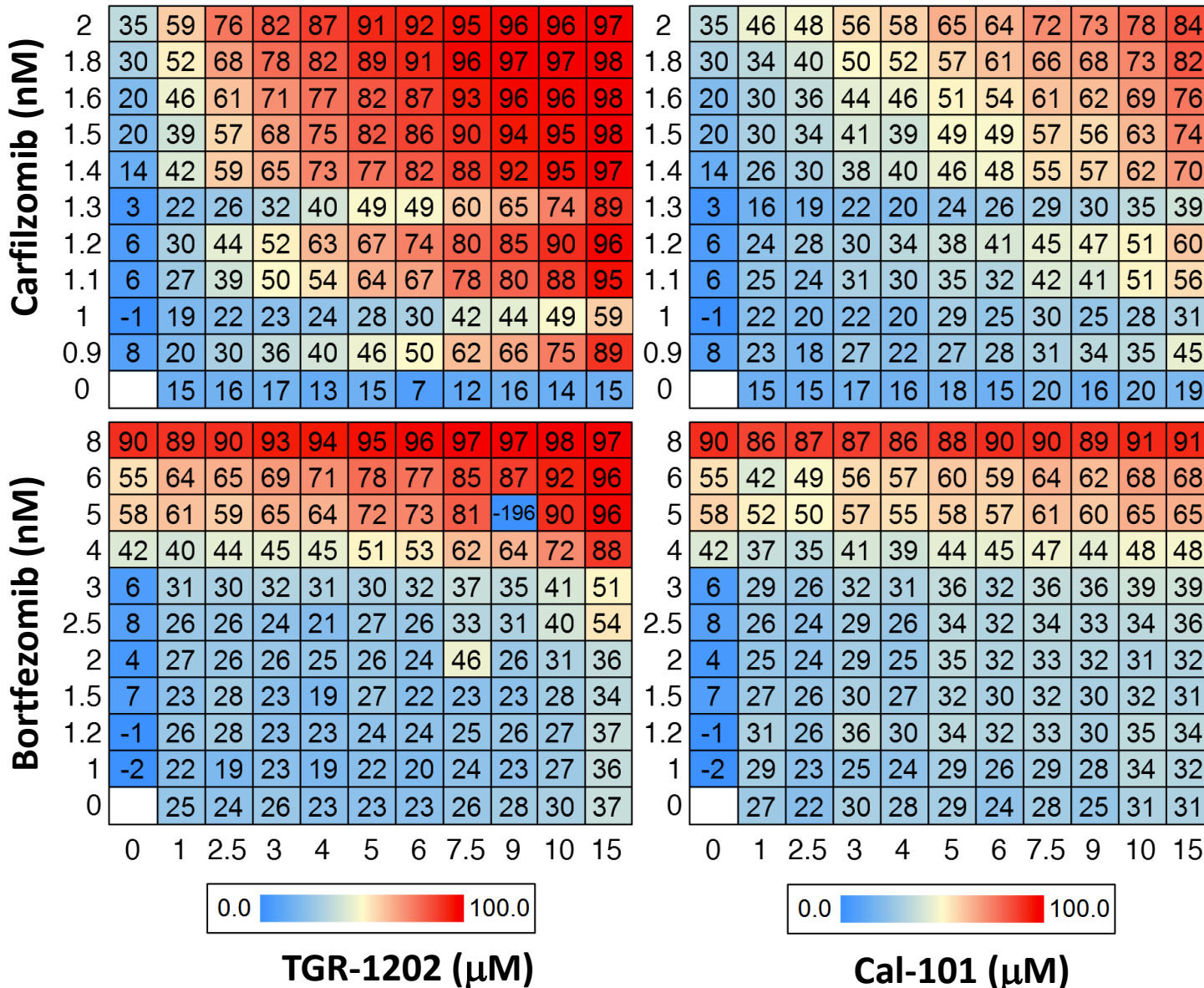


Suraweera, A., et al., Mol Cell, 2012  
Quy, P.N., et al., J Biol Chem, 2013  
Hutter, G., et al., Leukemia, 2012  
Zhang, Y., et al., Nature, 2014

Dibble CC and Cantley LC.  
Trends Cell Biol, 2015

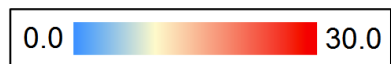
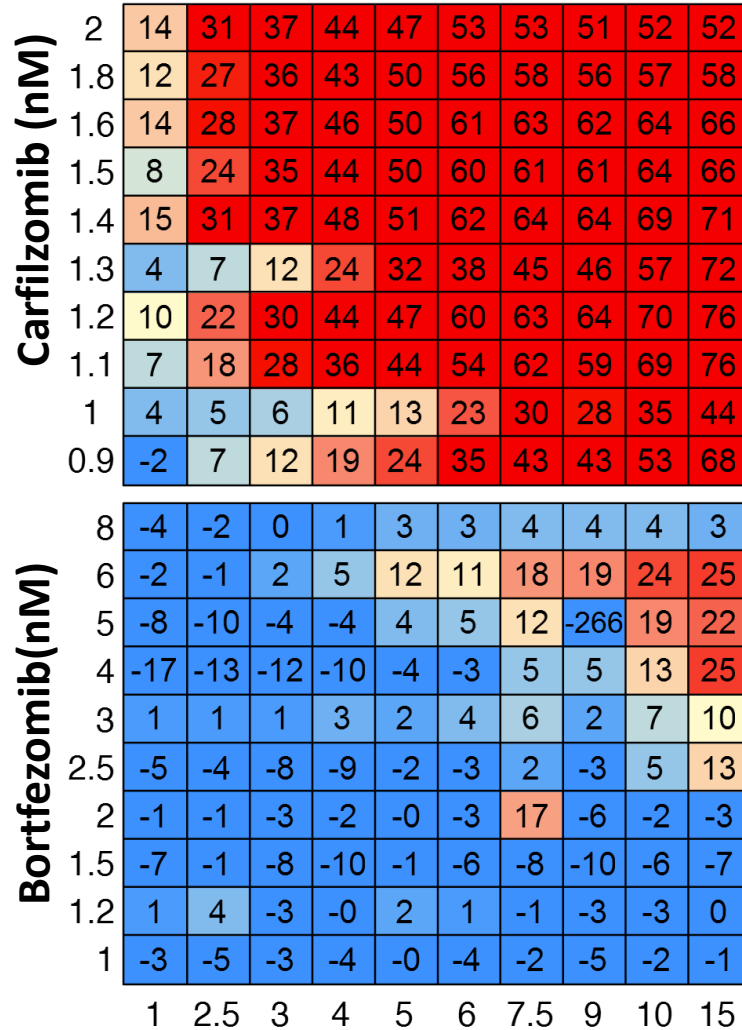
# PI3K $\delta$ Inhibitors and Proteasome Inhibitors Synergistically Inhibit DLBCL

## Observed Inhibition in the DLBCL cell line LY10

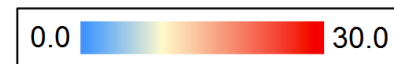
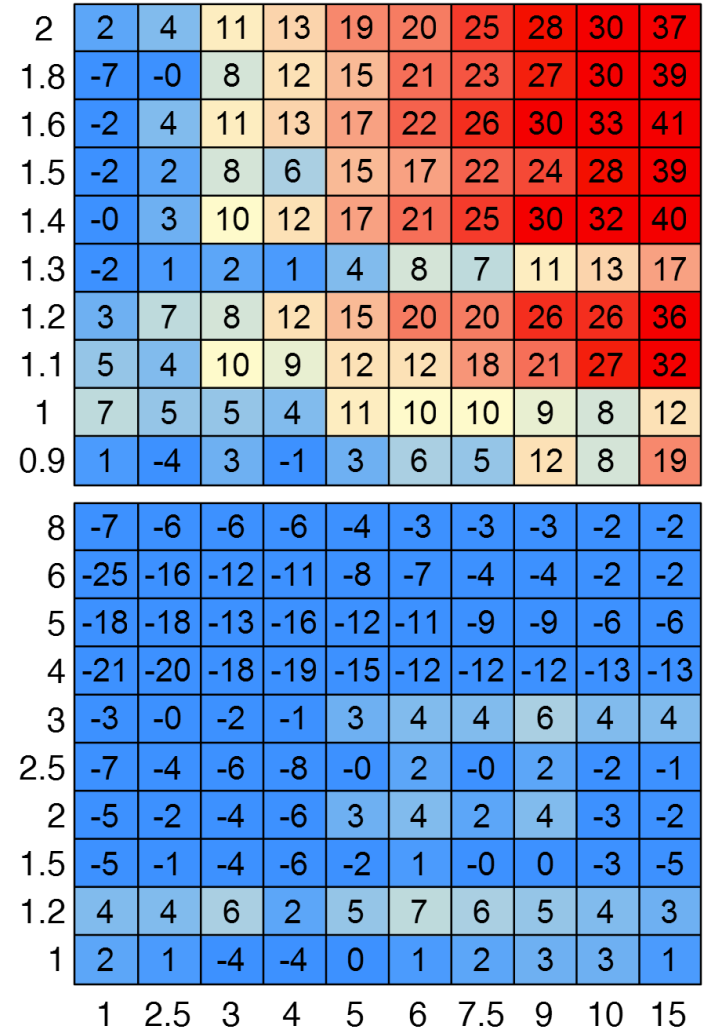


# Dual Inhibition of PI3K $\delta$ and Proteasome Is Most Synergistic with TG&Cfz Followed by Cal&Cfz > TG&Bz > Cal&Bz

Excess Over BLISS (EOB) in the DLBCL cell line LY10

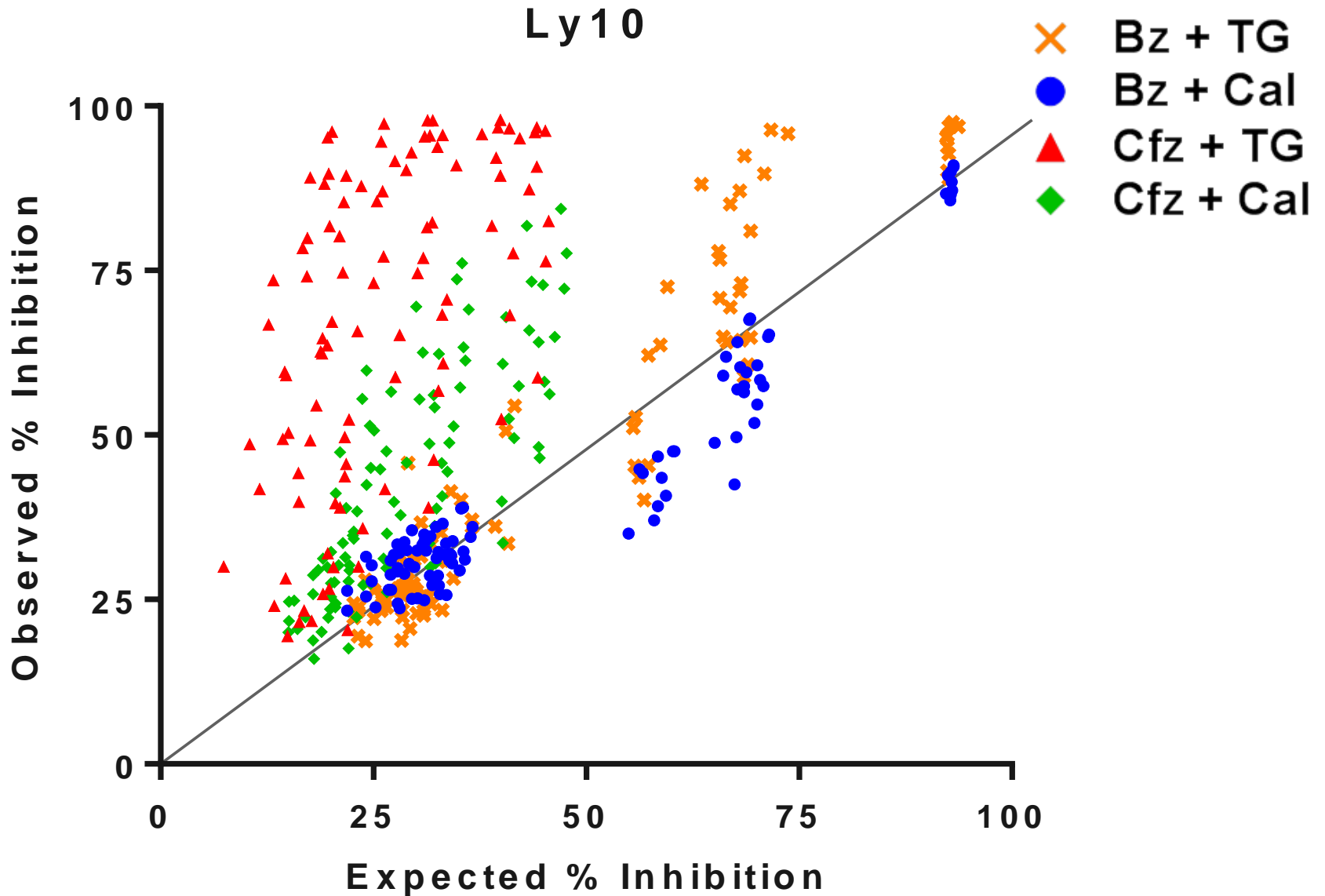


TGR-1202 ( $\mu\text{M}$ )

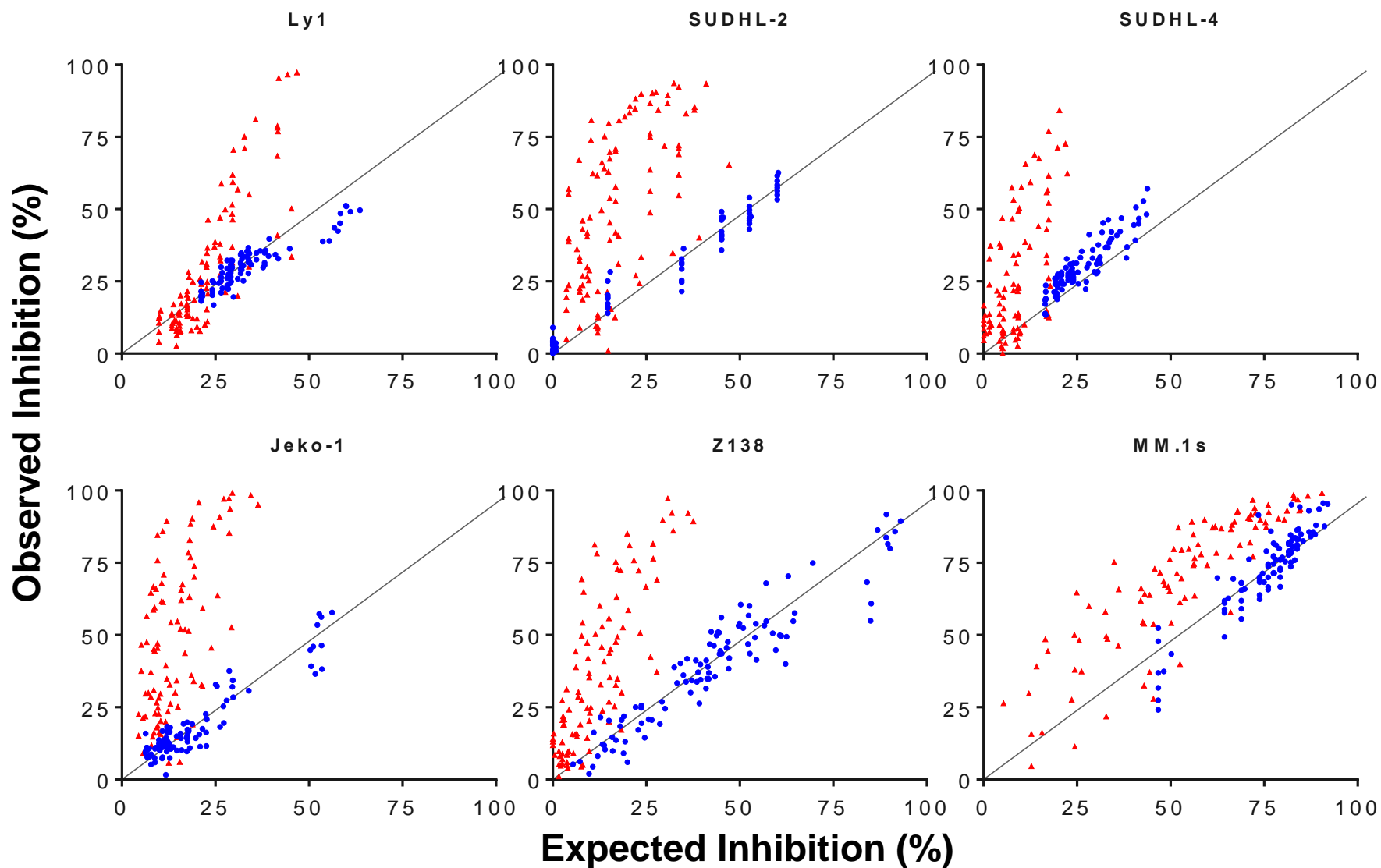


Cal-101 ( $\mu\text{M}$ )

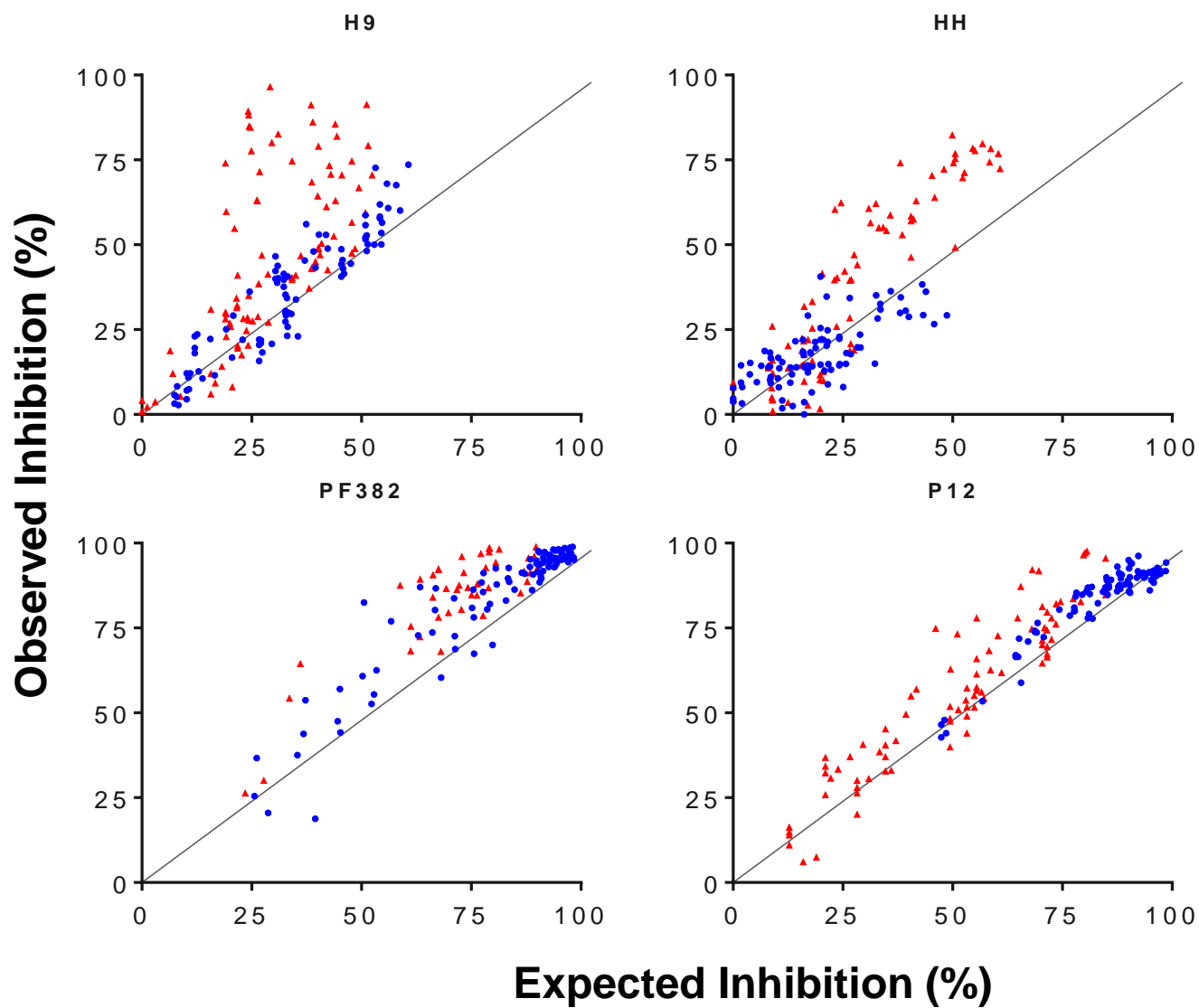
# Dual Inhibition of PI3K $\delta$ and Proteasome Is Most Synergistic with TG&Cfz Followed by Cal&Cfz > TG&Bz > Cal&Bz



# TGR-1202&Carfilzomib Is the Most Synergistic Combination in DLBCL, Mantle Cell Lymphoma, and Multiple Myeloma

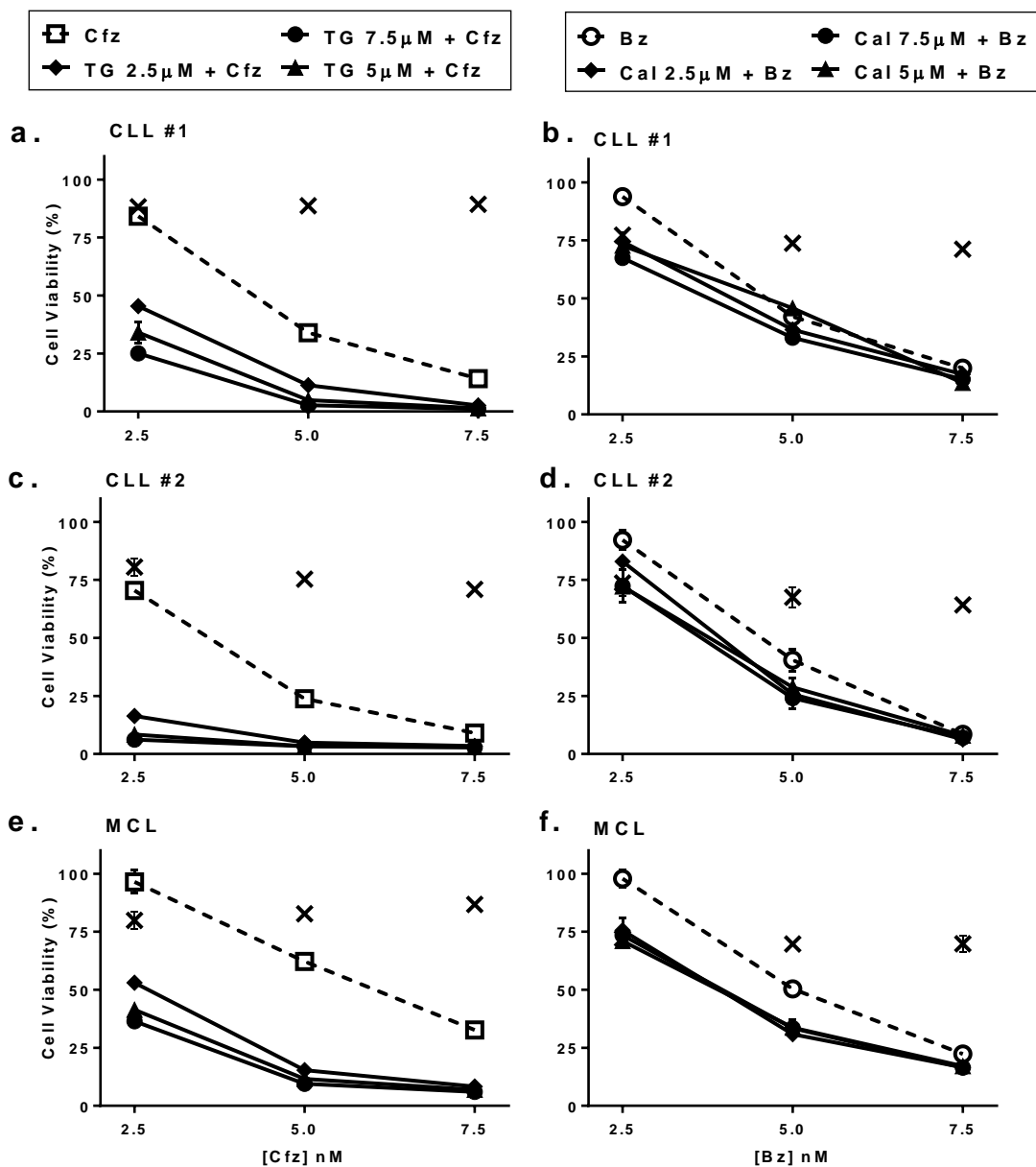


# TGR-1202&Carfilzomib Is the Most Synergistic Combination in T Cell Lymphoma

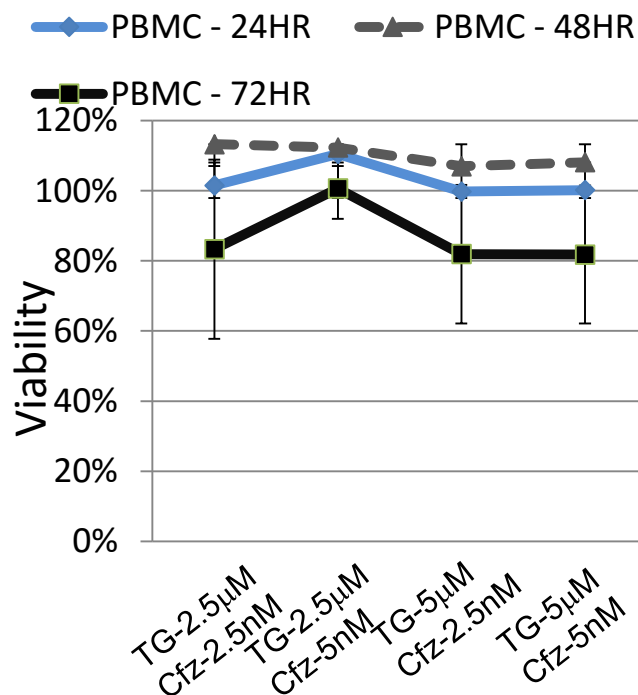




# TGR-1202 and Carfilzomib Are Synergistic in Primary CLL and MCL Cells but Not Toxic to Healthy Lymphocytes

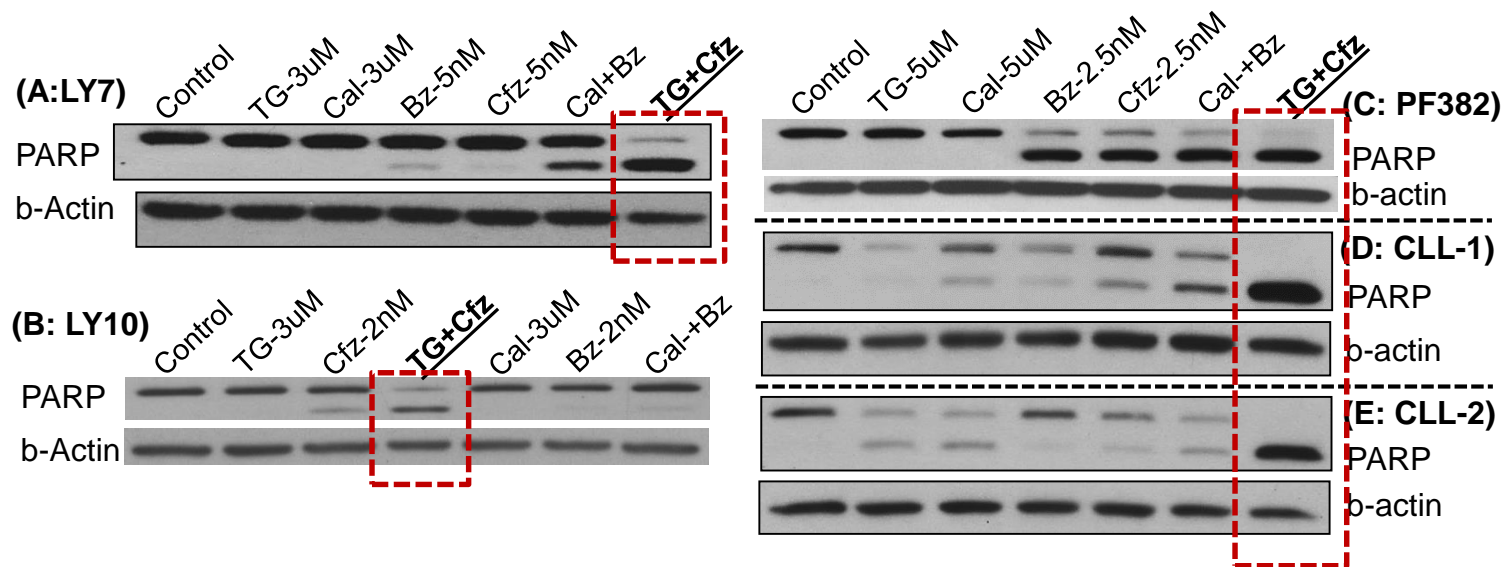


## Healthy lymphocytes

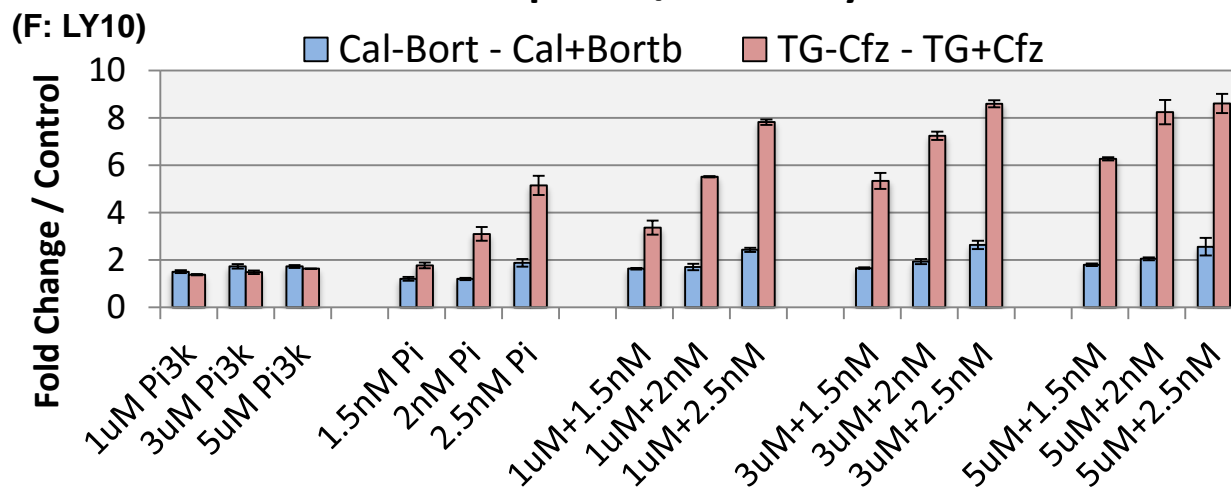


# TGR-1202 and Carfilzomib Synergistically Induce Apoptosis in Lymphoma Cell Lines and Primary Lymphoma Cells

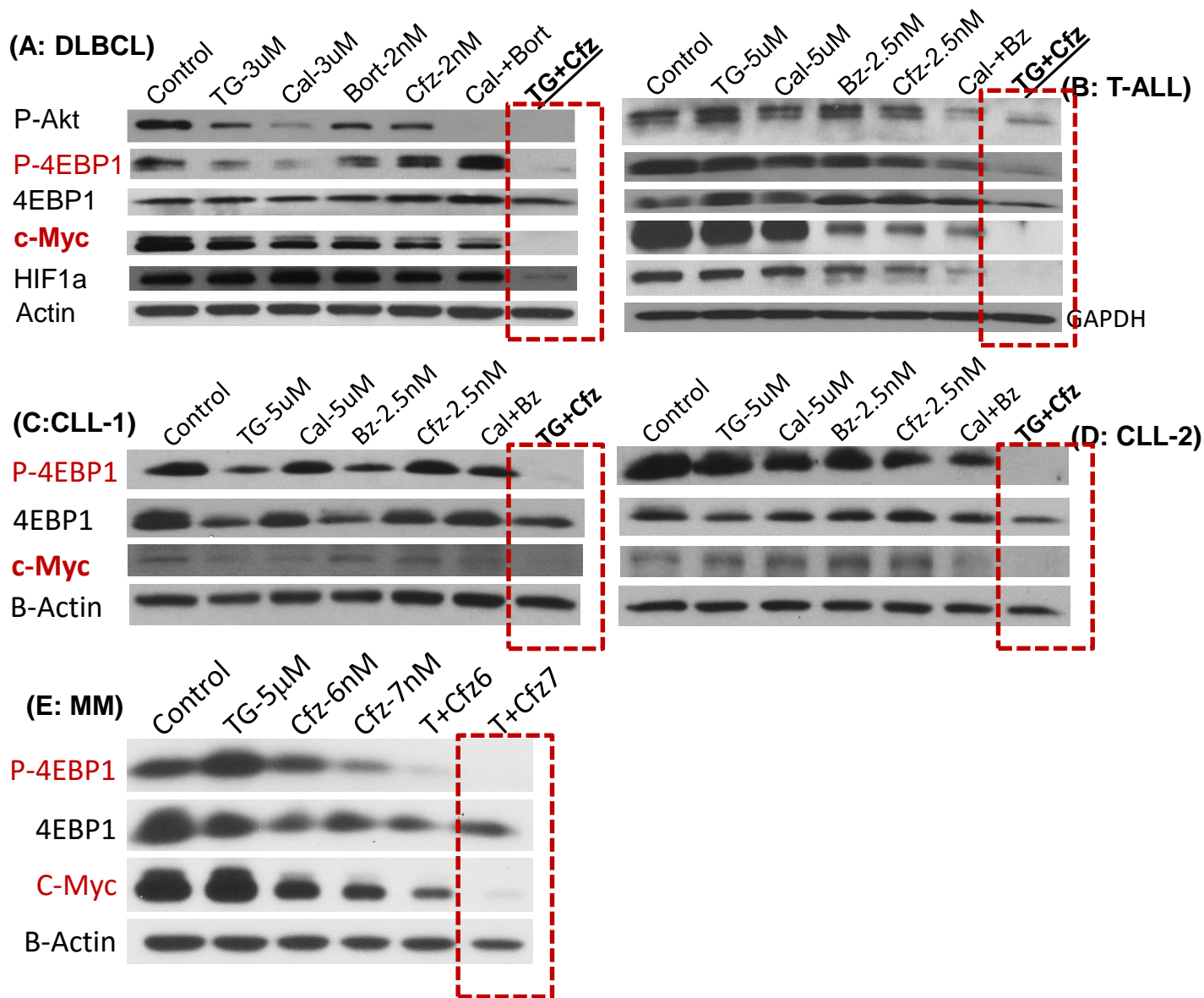
## PARP Cleavage



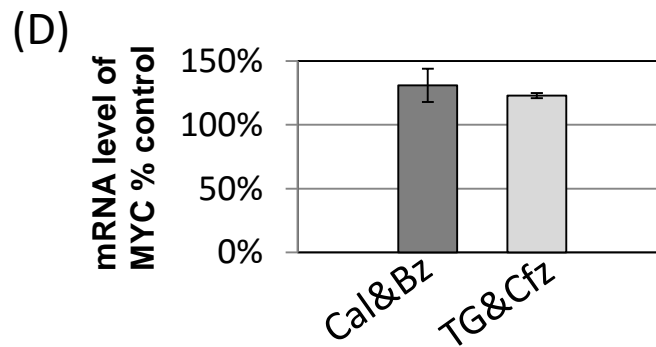
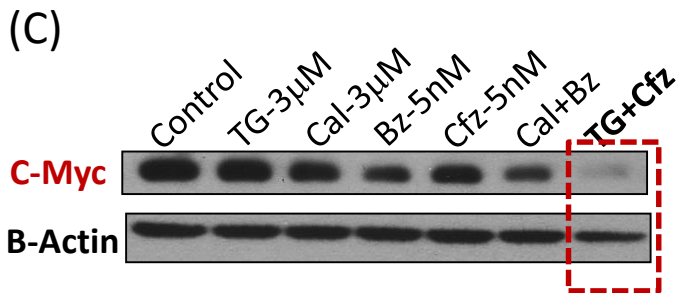
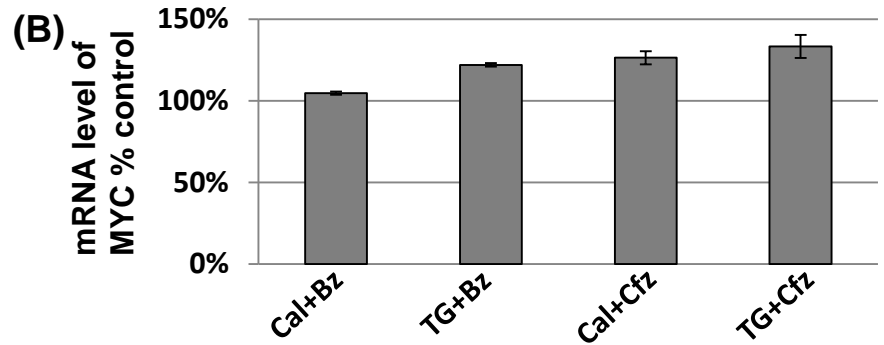
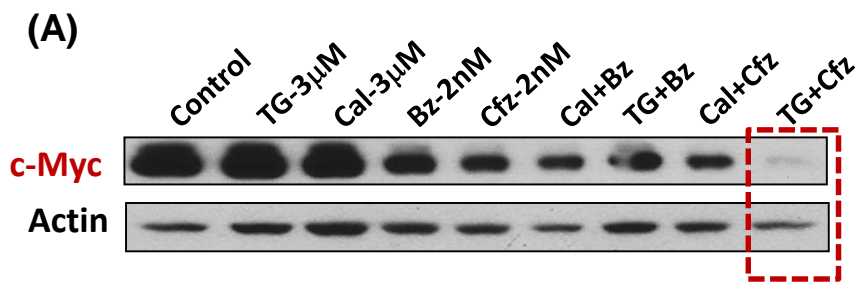
## Caspase 3/7 Activity



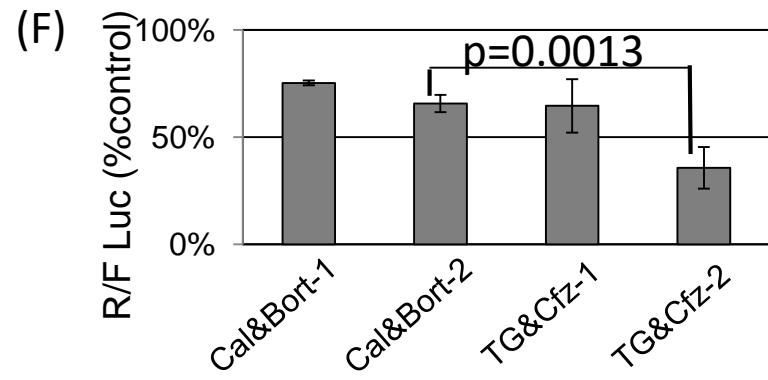
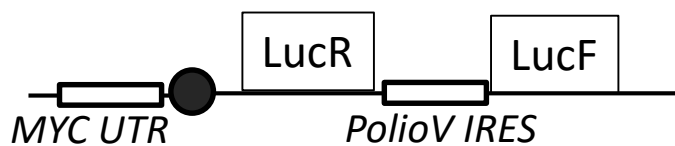
# TGR-1202 and Carfilzomib Synergistically Inhibit Phosphorylation of 4EBP1 and Expression of c-Myc



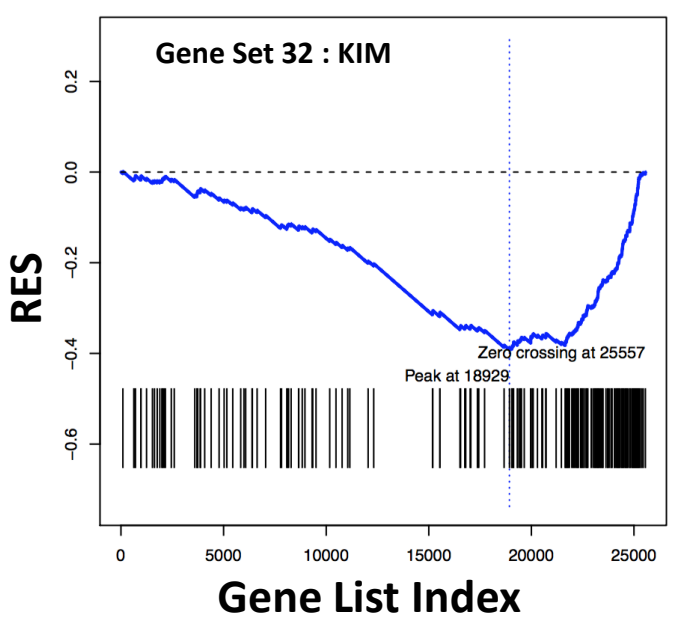
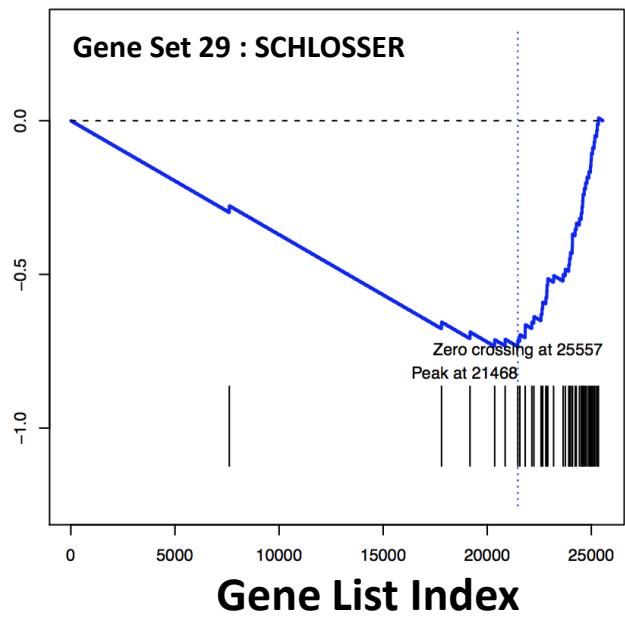
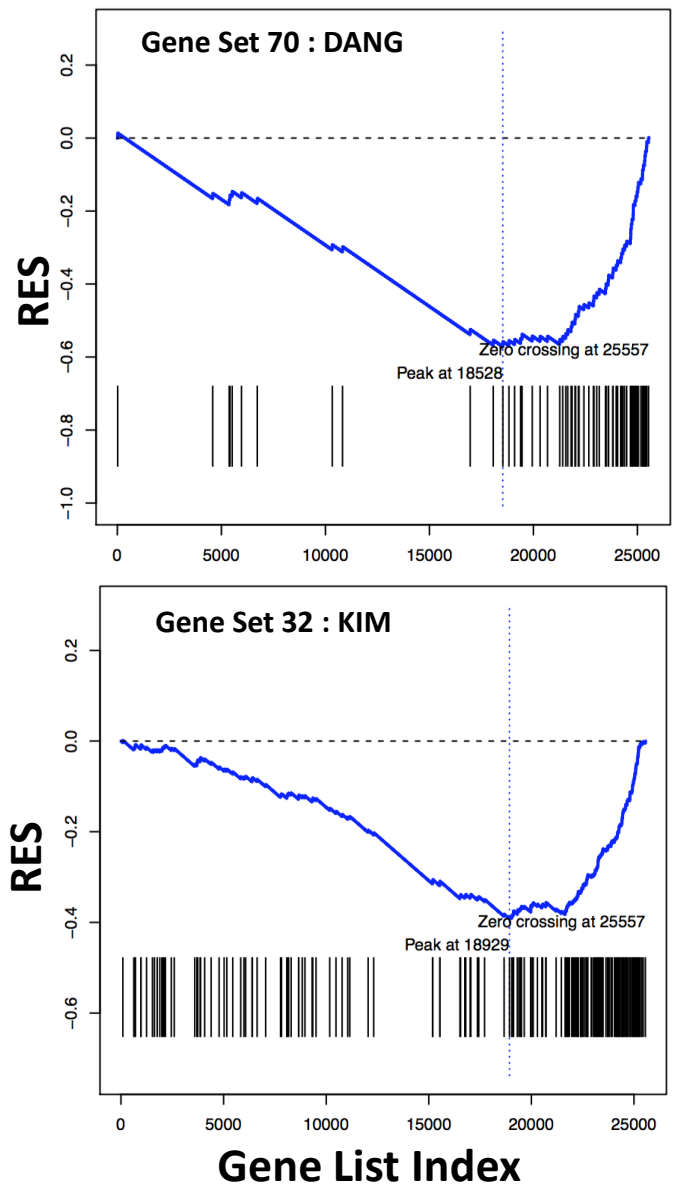
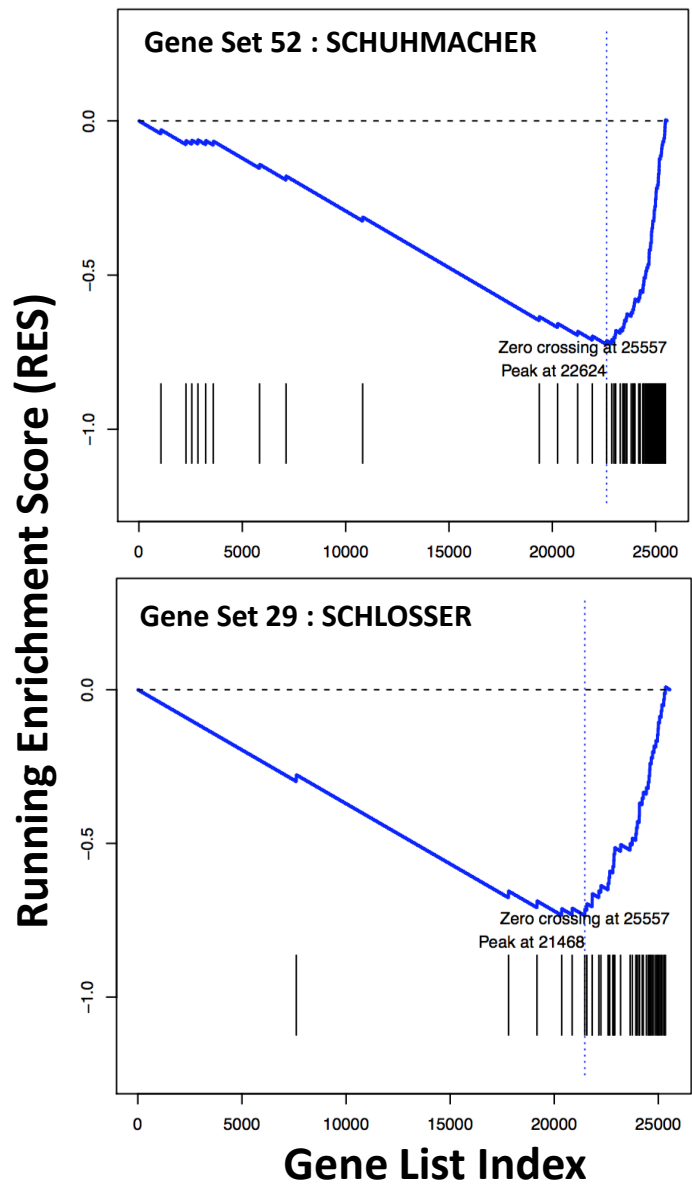
# TGR-1202 and Carfilzomib in Combination Inhibit Cap Dependent Translation of c-Myc in DLBCL



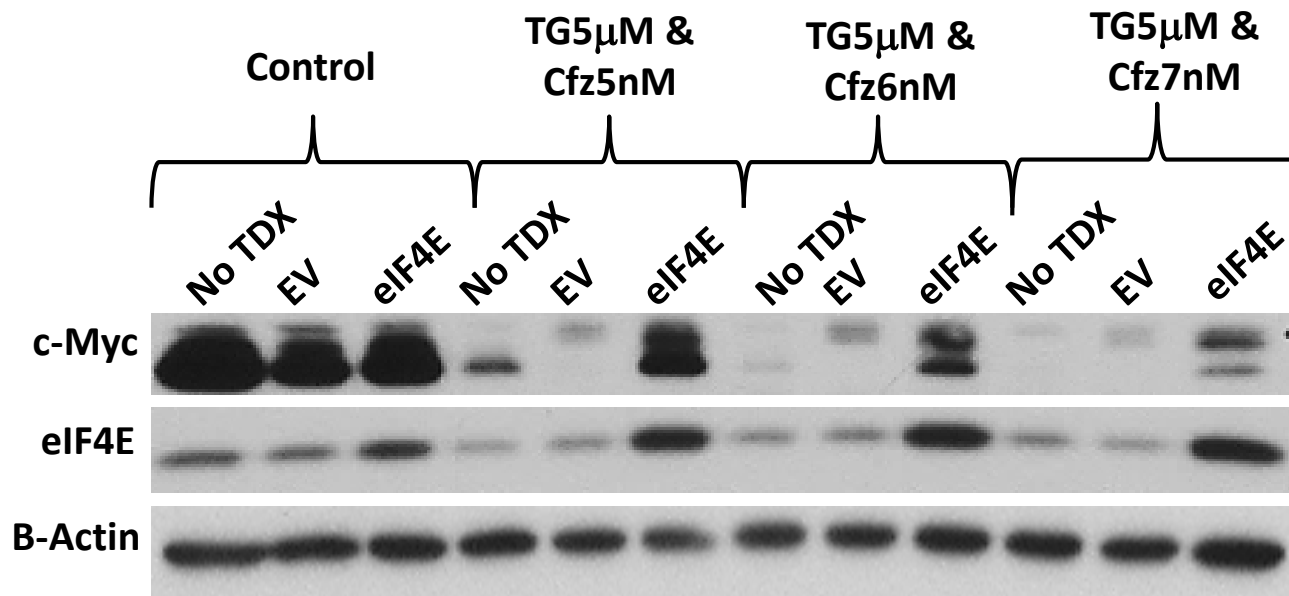
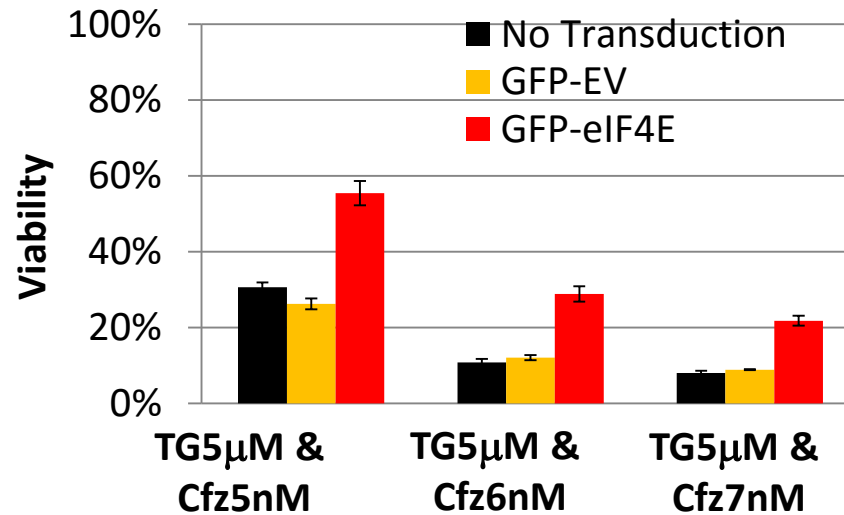
## (E) Cap dependent translation of Myc



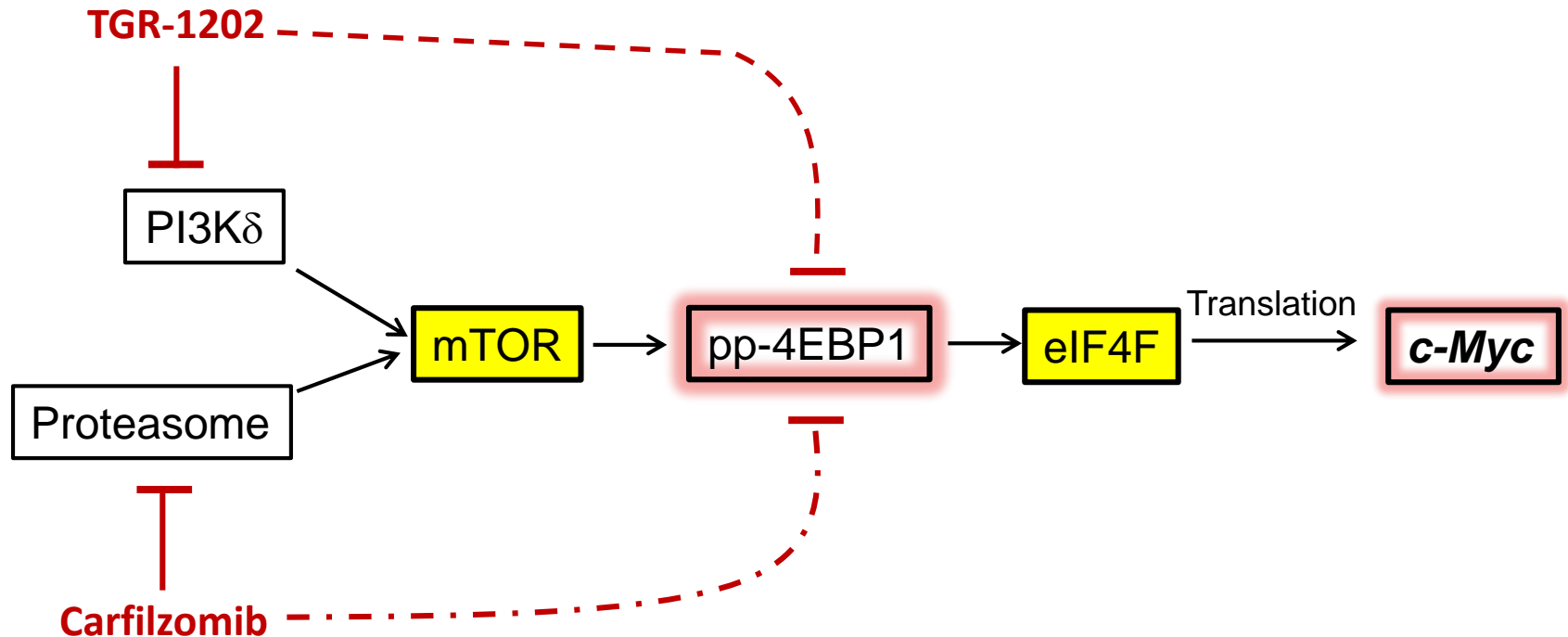
# TGR-1202 and Carfilzomib in Combination Inhibit the c-Myc Transcription Program in DLBCL



# Overexpression of eIF4E Suppresses the Synergistic Cytotoxicity of TGR-1202 and Carfilzomib and Increases the Protein Level of c-Myc



# Silence c-Myc through Simultaneous Targeting of the PI3K $\delta$ and Proteasome Pathways



- Optimize c-Myc-silencing therapy by targeting phosphorylation of 4EBP1
- Phase I/II clinical trial of TGR-1202 and carfilzomib in relapsed and refractory lymphoma

# *Thank you!*

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