

# Development of p97 AAA ATPase inhibitors

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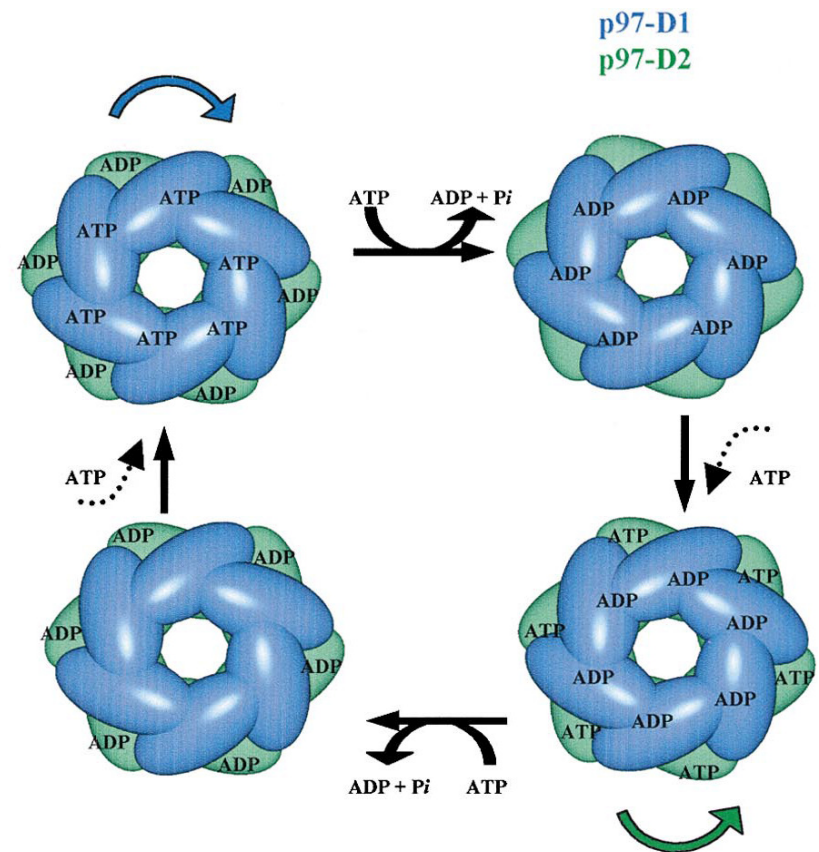
**Vsevolod Peshkov**

***Wipf Group Research Topic Seminar***

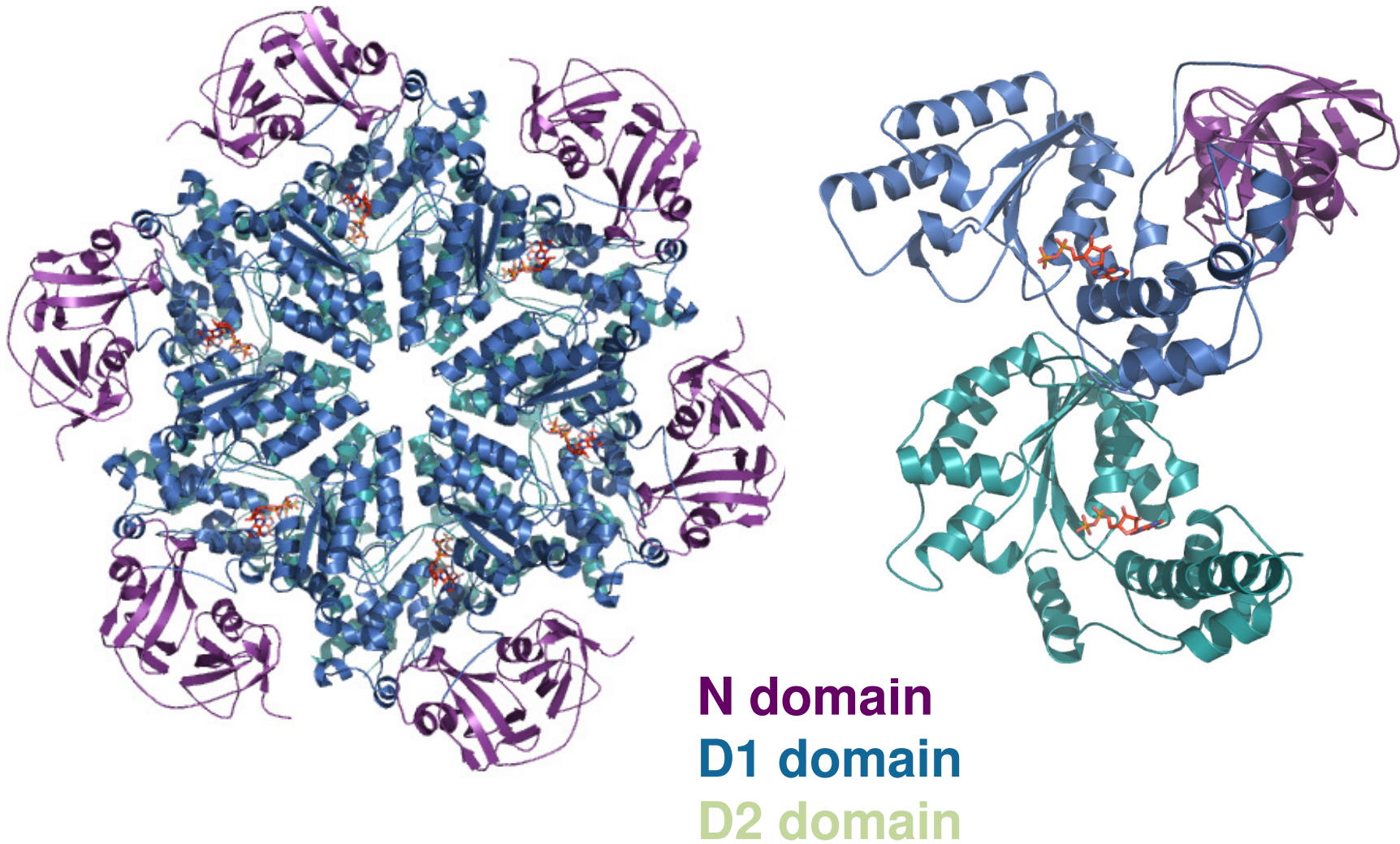
***03-29-2014***

# AAA proteins

- p97 is a member of AAA proteins family
- AAA stands for ATPases Associated with diverse cellular Activities. AAA proteins are involved in processes such as assembly, operation and disassembly of protein complexes, protein degradation, membrane fusion, signal transduction, DNA replication, regulation of gene expression *etc.*
- The quaternary structure of AAA ATPases possesses homo-oligomeric complexes featuring a ring-shaped structure with a central pore acting as a molecular motor that utilizes ATP binding and hydrolysis to changes the conformational states in order to act upon a target substrate

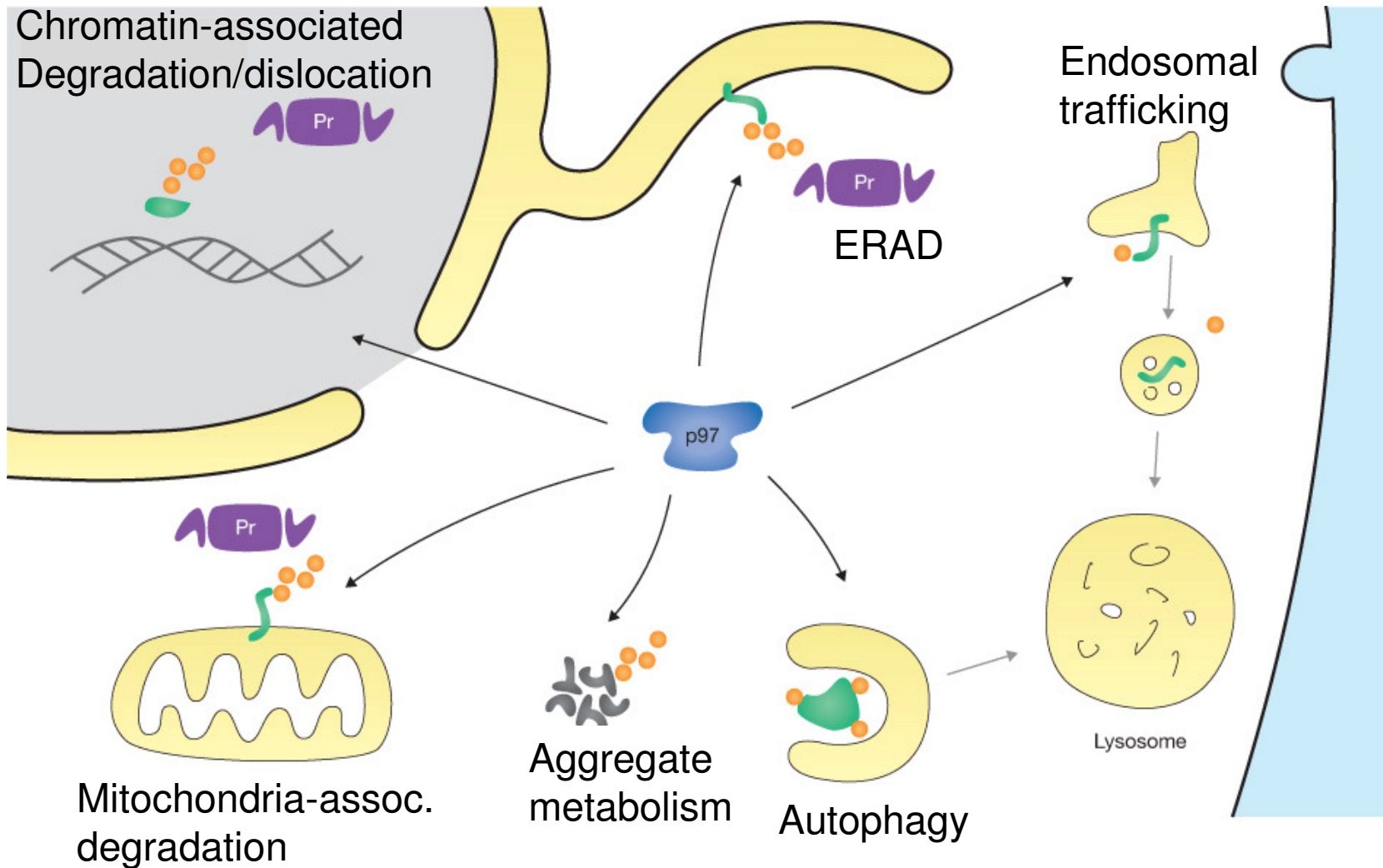


# p97 structure



X. Zhang *et al. Molecular Cell*, 2000, 6, 1473

# Cellular roles of p97

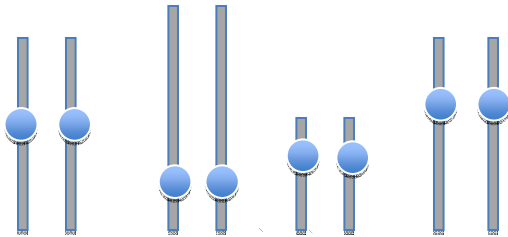


**Green - target substrates; Pr - proteasome; orange - ubiquitin**

H. Meyer, M. Bug, S. Bremer *Nature Cell Biology*, 2012, 14, 117

# p97 and cancer

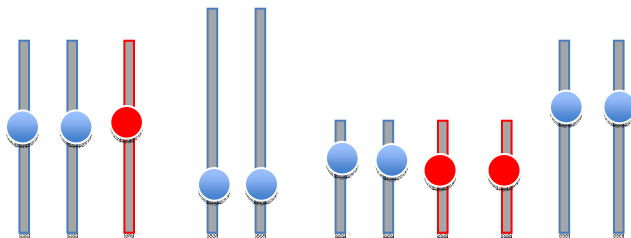
**NORMAL**



**Properly balanced  
protein production**

**Normal N of chromosomes**

**CANCER**



**Unbalanced  
protein  
production**

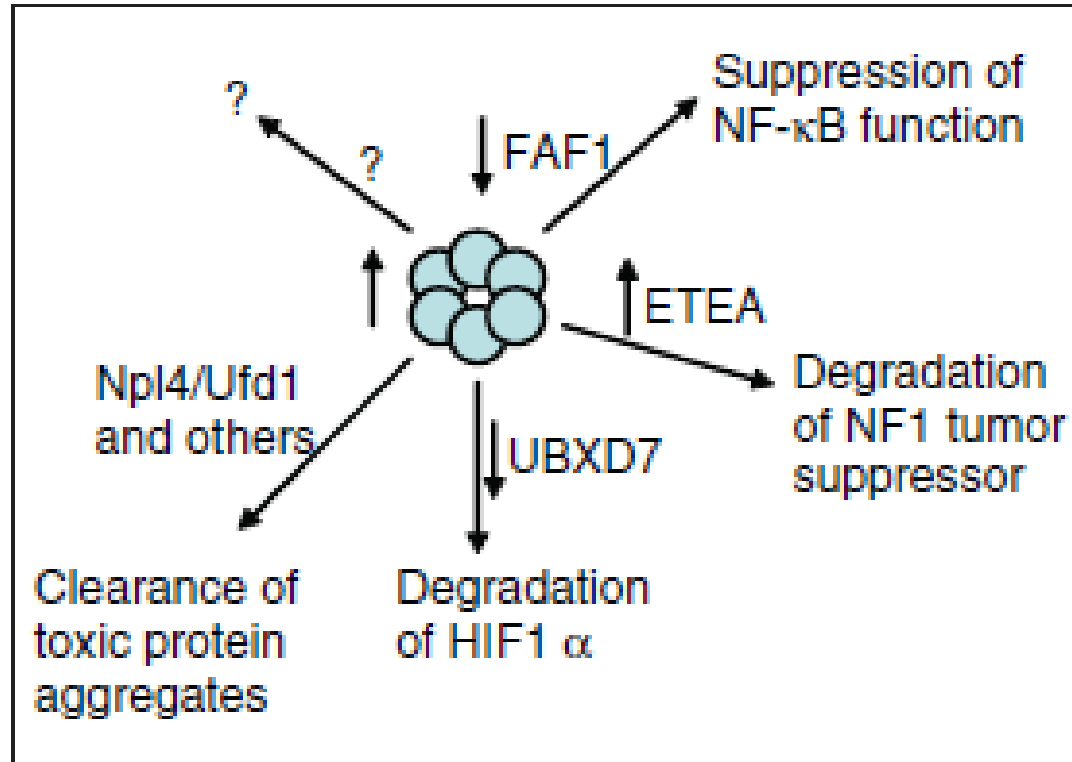


**Protein homeostasis  
systems are overloaded.  
p97 is up-regulated by  
protein damage-induced  
stress signals.**

**Excess of chromosomes**

D. S. Haines *Genes & Cancer*, 2010, 1, 753

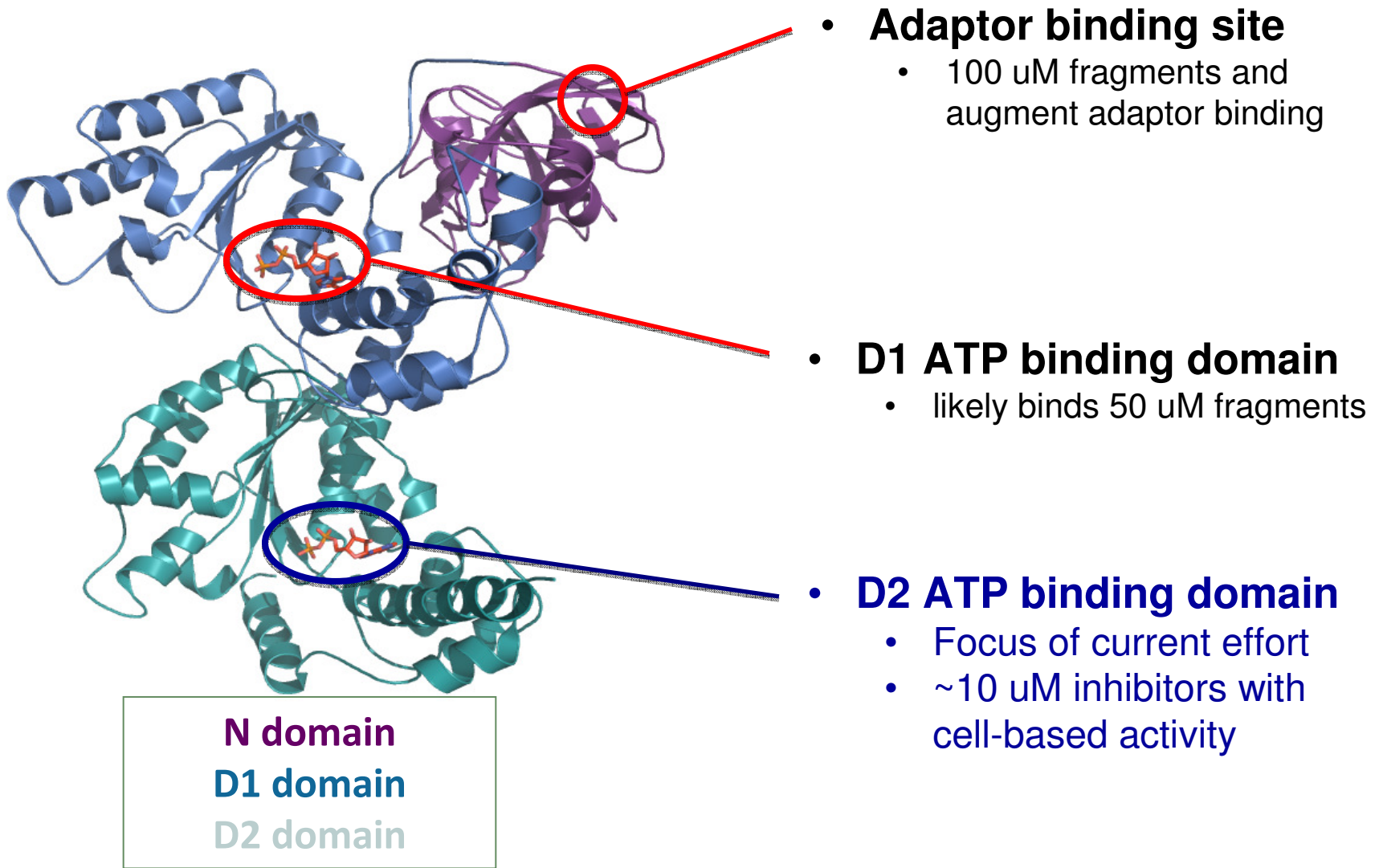
# p97 and cancer



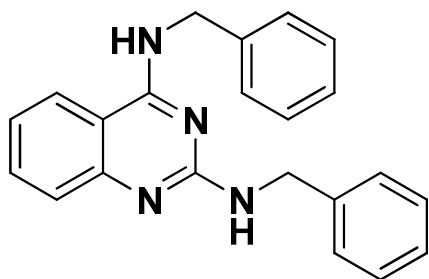
In addition, p97 and/or adaptors have been implicated in the direct regulation of several key cancer-relevant proteins

D. S. Haines *Genes & Cancer*, 2010, 1, 753

# p97 binding sites



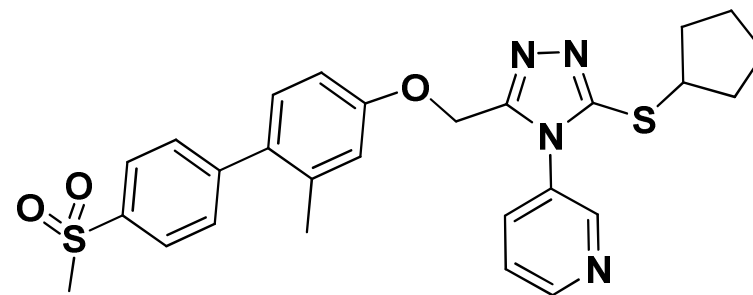
# p97 inhibitors in literature



***N*<sup>2</sup>,*N*<sup>4</sup>-dibenzylquinazoline-2,4-diamine (DBeQ)**

IC<sub>50</sub> = 1.6 μM (ADPglo)

T.-F. Chou *et al.* *Proc. Natl. Acad. Sci. USA*, **2011**, *108*, 4834



**NMS-873**

IC<sub>50</sub> = 0.03 μM (original assay)  
IC<sub>50</sub> = 0.008 μM (ADPglo)

P. Magnaghi *et al.* *Nat. Chem. Biol.*, **2013**, *9*, 548



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