



Development of Inhibitors of the AAA ATPase Chaperone p97

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Valosine Containing Protein (VCP)/p97

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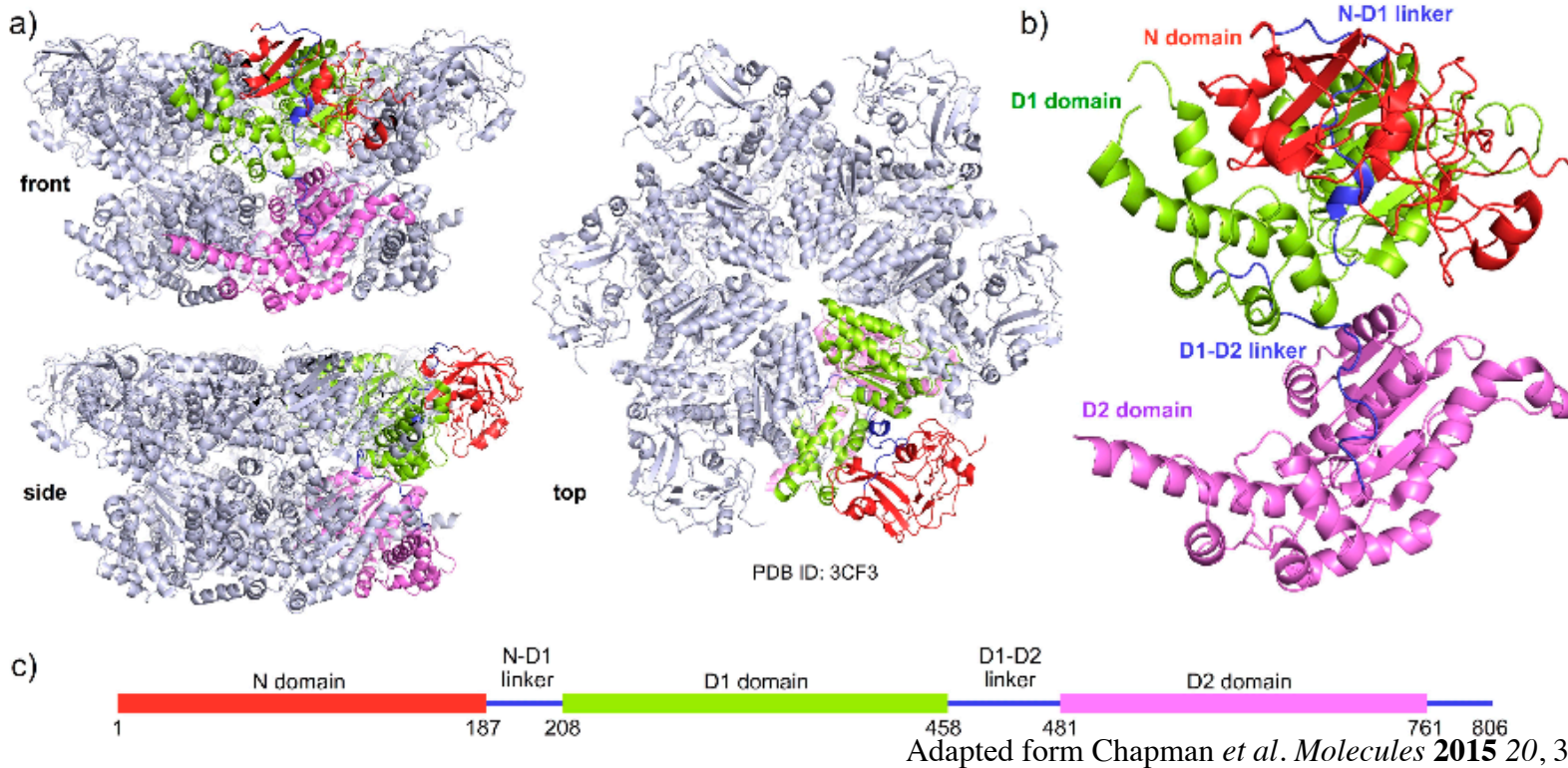
- One of the **most abundant** in eukaryotic cytosol, **account for >1%** cellular protein content
- A member of **AAA** (**A**TPases **A**ssociated with various cellular **A**ctivities) family of proteins
- An **enzymatic machine** that transforms the **chemical energy** produced by the hydrolysis of ATP **in to mechanical work**
- Linked to
 - Protein degradation
 - membrane fusion
 - transcription activation
 - cell cycle control
 - apoptosis
 - autophagy
 - general chaperone activity

Polucci *et al. J. Med. Chem.*, **2013**, *56*, 437-450 2



Structure and Function

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- A ring shaped **homo-hexamer**: comprised of **6 subunits**
- Each unit contains **3 domains**:
 - **N domain**: responsible for the interaction with cofactors and adaptor proteins
 - **D1 domain**: promotes hexamer assembly, has low hydrolytic activity
 - **D2 domain**: provides most of ATPase activity
- **Highly flexible**: global changes upon ATP binding and hydrolysis

3



Link with Cancer and Inhibition

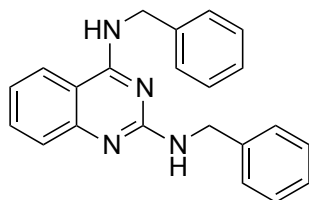
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“Its remarkable that a pathway as ubiquitous as protein quality control can be targeted to treat cancer”

Chapman *et al. Molecules*, **2015**, *20*, 2037.

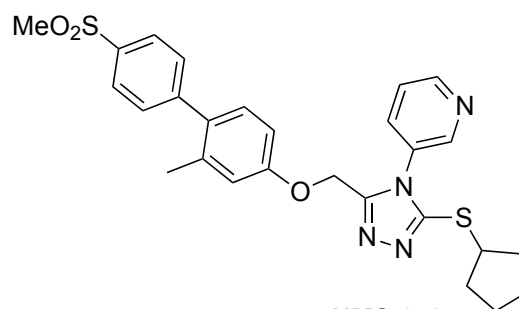
- ❑ Increasingly linked to cancer: **elevated VCP expression** reported in several tumors
- ❑ Mutations in the VCP gene are associated with several **human neurodegenerative diseases**

Inhibitors in the literature



N^2,N^4 -dibenzylquinazoline-2,4-diamine
(**DBeQ**)

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



NMS-873

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



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