Development of p97 AAA ATPase inhibitors

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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

p97 and cancer

**NORMAL**

Normal N of chromosomes

**Properly balanced protein production**

**CANCER**

Excess of chromosomes

**Unbalanced protein production**

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

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

- **Adaptor binding site**
  - 100 µM fragments and augment adaptor binding

- **D1 ATP binding domain**
  - Likely binds 50 µM fragments

- **D2 ATP binding domain**
  - Focus of current effort
  - ~10 µM inhibitors with cell-based activity
p97 inhibitors in literature

\[ N^2,N^4\text{-dibenzylguinazoline-2,4-diamine (DBeQ)} \]

\[ \text{IC}_{50} = 1.6 \, \mu\text{M (ADPglo)} \]


\[ \text{NMS-873} \]

\[ \text{IC}_{50} = 0.03 \, \mu\text{M (original assay)} \]
\[ \text{IC}_{50} = 0.008 \, \mu\text{M (ADPglo)} \]

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