Targeting the Molecular Chaperone Hsp90 in Cancer: What Does the Biology Tell Us?

Len Neckers

TAT 2011
Activity & Stability of Folded Proteins

Regular Folding Pathways

Molecular Chaperones

Quality Control of Misfolded Proteins

Activity & Stability of Folded Proteins

Hsp90
Why Hsp90?
Hsp90 senses environmental stress & coordinates cellular responses to promote survival.
Hsp90 clients include many mutated oncogenic kinases: Bcr-Abl, EGFR, MET, ALK…
Development of Hsp90 inhibitors

Hsp90 inhibitors in clinical trial

- 1970: Deboer, J. Antibiot., Geldanamycin
- 1994: PNAS
- 1999: ID Target 17-AAG, 17-DMAG
- 2004: IPI-504
- 2005: BIIB021
- 2006: SNX-5422, AUY922, KW-2478
- 2007: IPI-493, BIIB028, STA-9090, XL888
- 2008: AT13387, HSP990
- 2009: MPC-3100, ABI-01
- 2010: Debio 0932, PU-H71, DS-2248
Published Hsp90 inhibitor clinical trials

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>3</td>
</tr>
<tr>
<td>2006</td>
<td>2</td>
</tr>
<tr>
<td>2007</td>
<td>4</td>
</tr>
<tr>
<td>2008</td>
<td>6</td>
</tr>
<tr>
<td>2010</td>
<td>10</td>
</tr>
</tbody>
</table>
Conclusions to date based on published data:
(tanespimycin (17AAG), alvespimycin (17DMAG), retaspimycin (IPI-504))

- MTD and toxicity are strongly influenced by schedule

- Hsp90 inhibitor + trastuzumab is well tolerated and has anti-tumor activity in patients with HER2+ breast cancer whose tumors have progressed on trastuzumab alone (Modi et al., J Clin Oncol, 2007)

- Hsp90 inhibitor + sorafenib has clinical activity in kidney cancer and melanoma (Vaaishampayan et al., Clin Cancer Res, 2010)

- Single agent activity seen in 3 of 7 evaluable patients with advanced acute myeloid leukemia (Lancet et al., Leukemia, 2010)

- Hsp90 inhibitor +/- bortezomib has clinical activity and reduced peripheral neuropathy in patients with relapsed/refractory multiple myeloma (Richardson et al., Br J Haematol, 2010, x2)

- Single agent activity seen in patients with NSCLC, particularly those with ALK rearrangements (Sequist et al., J Clin Oncol, 2010)
Complex twist & turns of the chaperone cycle

Chaperone-dependent E3 ubiquitin ligase CHIP mediates a degradative pathway for c-ErbB2/Neu.
Xu et al., Proc Natl Acad Sci U S A, 2002

Regulation of Hsp90 client proteins by a Cullin5 RING E3 ubiquitin ligase.
Ehrlich et al., Proc Natl Acad Sci U S A, 2009

Hsp90 inhibitors are concentrated and retained in tumor.

---

Eiseman et al., Cancer Chemotherapy and Pharmacology, 2004

Continuous daily dosing?
Hsp90 inhibitors promote rapid degradation of ErbB2 but not of WT EGFR

Untreated        GA (2 µM, 22 hrs)

ErbB2 expression in SKBR3 cells

Xu et al., J Biol Chem, 2001

Chavany et al., J Biol Chem, 1996
HER2+ Breast Cancer: 17-AAG + Herceptin in Patients Who Progressed on Herceptin Alone

Response rate: 26%; overall clinical benefit rate: 63%

S. Modi et al. ASCO 2008
(Cliff Hudis, MSKCC)
Hsp90 inhibitors abrogate TKI resistance
Hsp90 Inhibitors Destabilize Bcr-Abl Tyrosine Kinase

80 1 3 8 11 h post GA

A
Bcr-Abl WT

Bcr-Abl T315I

IB

IB

β
c

% Survival

Days after BMT

Placebo
Imatinib
IPI-504 (50 mg/kg)
Imatinib+IPI-504 (50mg/kg)
IPI-504 (100mg/kg)

% Survival

Days after BMT

Placebo
Imatinib
IPI-504 (50 mg/kg)
Imatinib+IPI-504 (50mg/kg)
IPI-504 (100mg/kg)

Peng et al., Blood, 2007
An et al., Cell Growth Differ, 2000
Blagosklonny et al., Leukemia, 2001
Hsp90 Inhibitors Destabilize Bcr-Abl Tyrosine Kinase

“Sequencing revealed only WT Bcr-Abl in AUY922-resistant clones”

FROM: Tauchi et al., Oncogene, 2011
Combined effects of novel heat shock protein 90 inhibitor NVP-AUY922 and nilotinib in a random mutagenesis screen
Hsp90 Inhibitors Destabilize EGFR Kinase Domain Mutants

**Exon 20 insertion mutations**

Xu et al., Br J Cancer, 2007

**T790M mutations**

Shimamura et al., Cancer Res, 2008

Shimamura et al., Cancer Res, 2008
Hsp90 Inhibitors Destabilize NPM-ALK in ALCL

Bonvini et al., Cancer Res, 2002
EML4-ALK is very sensitive to Hsp90 inhibition.

- Sasaki et al., Cancer Res, 2010
- Chen et al. Cancer Res, 2010
- Normant et al., Oncogene, 2011
Hsp90 inhibitors abrogate TKI resistance

- By targeting TKI resistance mutations
Escape from c-MET TKI

Reactivation of HER1/2/3 is mediated by PKCδ

Wang et al., Cell Cycle, 2009
Escape from HER1/2 TKI

Pashtan et al., Cell Cycle, 2009
Escape from BRAF-V600E TKI

0 4 16 40 hrs post GA

Schulte et al., J Biol Chem, 1995

Montagut et al., Cancer Res, 2008
Escape from BRAF-V600E TKI

Montagut et al., Cancer Res, 2008
Can Hsp90 be made more sensitive to inhibitors?

Mollapour et al., Mol. Cell, 2010
Inhibition of Wee1 sensitizes cells to Hsp90 inhibitors

Mollapour et al., Mol. Cell, 2010
Non-phospho *hsp90* yeast mutants display enhanced sensitivity to geldanamycin.
Wee1 inhibition enhances cancer cell sensitivity to the Hsp90 inhibitor 17AAG

PC3 cells

- WEE1inhib. II
+ WEE1inhib. II

HeLa cells

- WEE1inhib. II
+ WEE1inhib. II

Apoptosis (%) vs. 17AAG (nM)
Contributors

Urologic Oncology Branch-NCI
Mehdi Mollapour
Shinji Tsutsumi
Wanping Xu
Brad Scroggins
Srinivas Vourganti

Radiation Oncology Branch-NCI
William G. Stetler-Stevenson
Dimitra Bourboulia
Sandra Jensen-Taubman

University of Sussex, UK
Laurence Pearl
Chris Prodromou

University of Kansas
Alison C. Donnelly (NIH)
Brian S. Blagg

Instituto di Chimica del Riconoscimento Molecolare, CNR, Milano, Italy
Giorgio Colombo
Giulia Morra

King’s College London, UK
Barry Panaretou