Drugs to reshape mutant TP53

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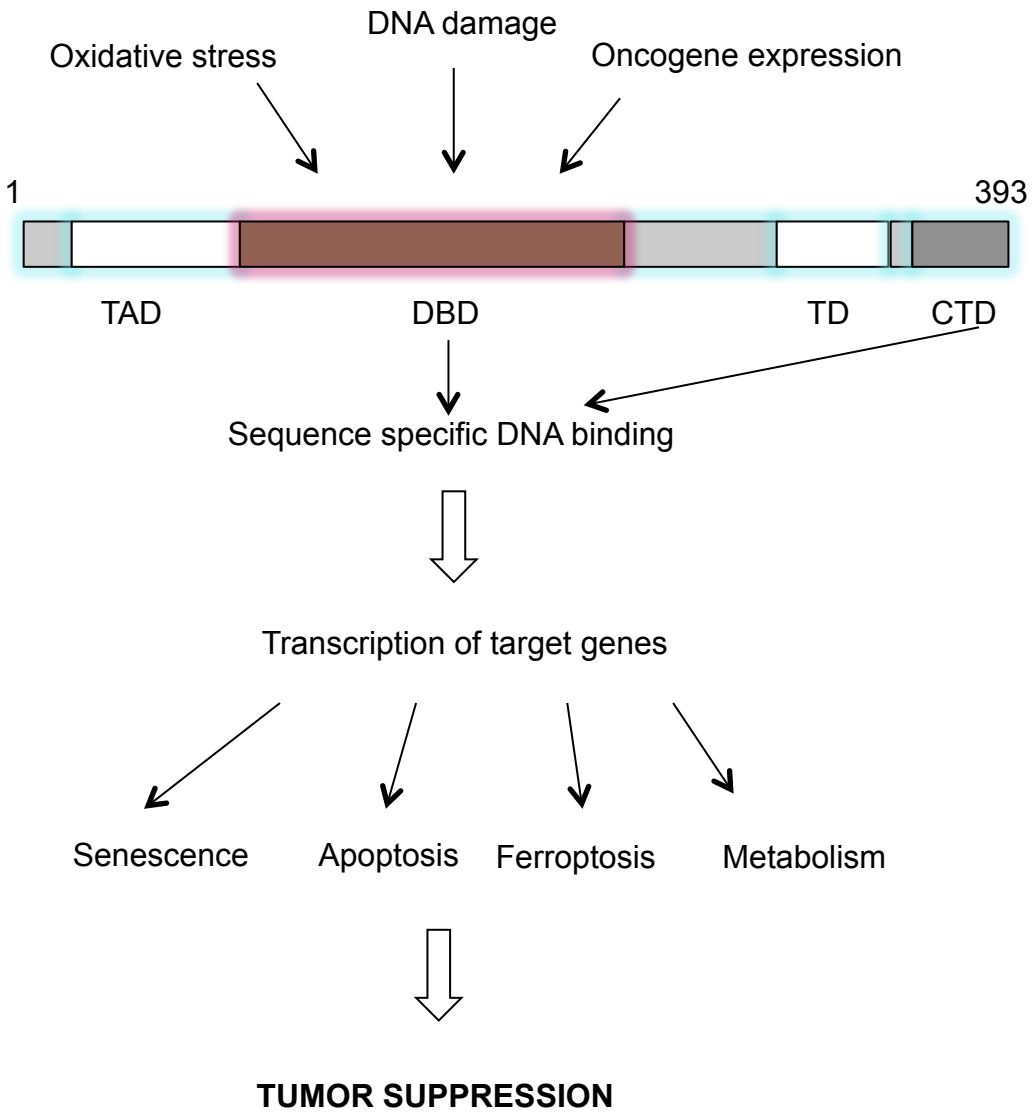
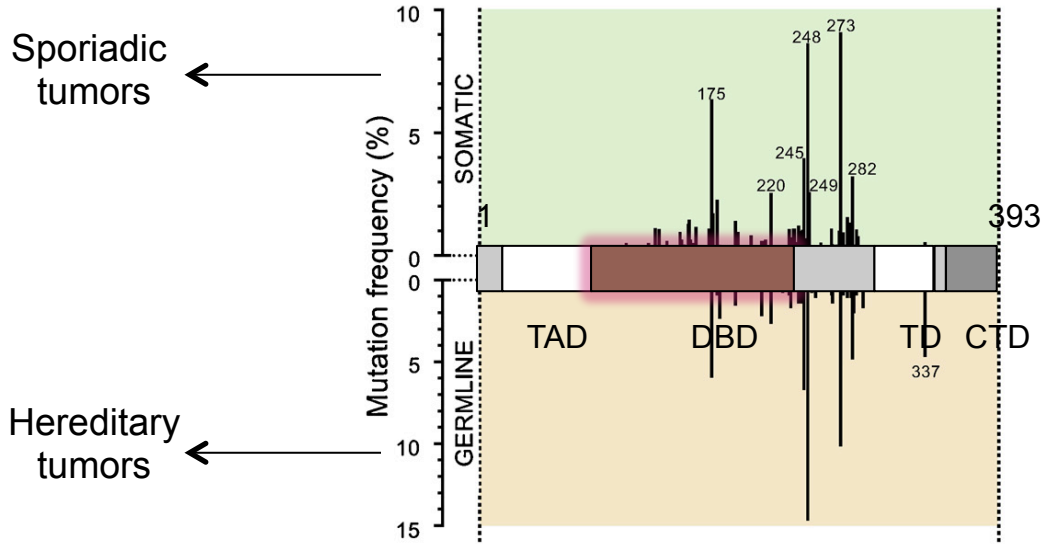
LFS Conference 2018 UK
The George Pantziarka TP53 Trust

*TP*53 structure and function

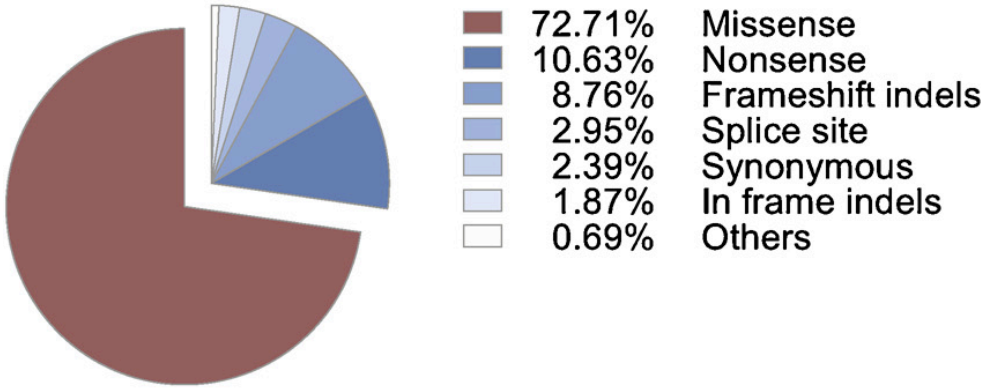


*TP*53 mutations in cancer patients

Distribution of somatic and germline mutations in cancer

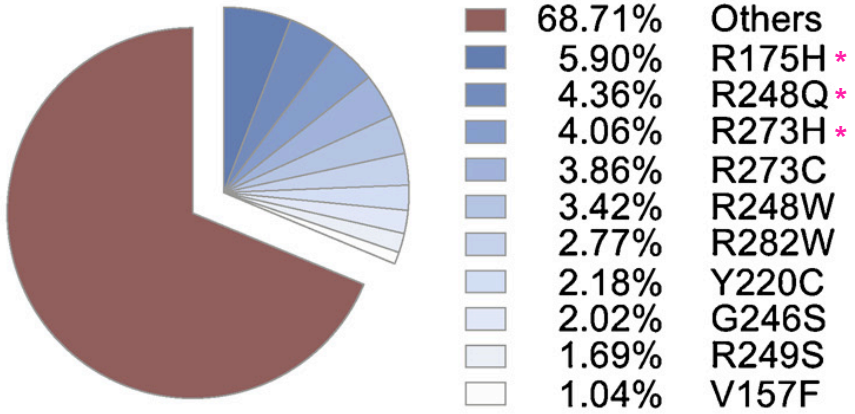


Frequency of *TP*53 somatic cancer mutation types

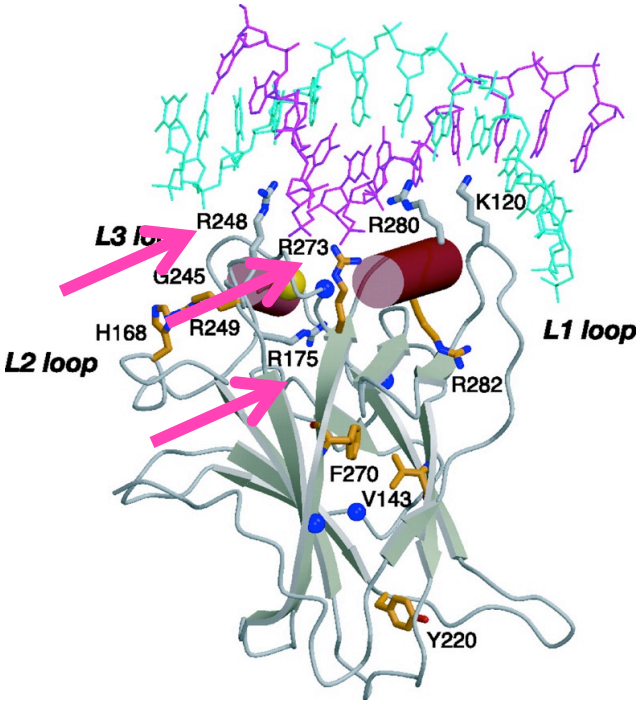


Adapted from Stiewe & Haran Drug Resistance Update, 2018

*TP*53 missense mutations in cancer patients



Stiewe & Haran, Drug Resistance Update, 2018

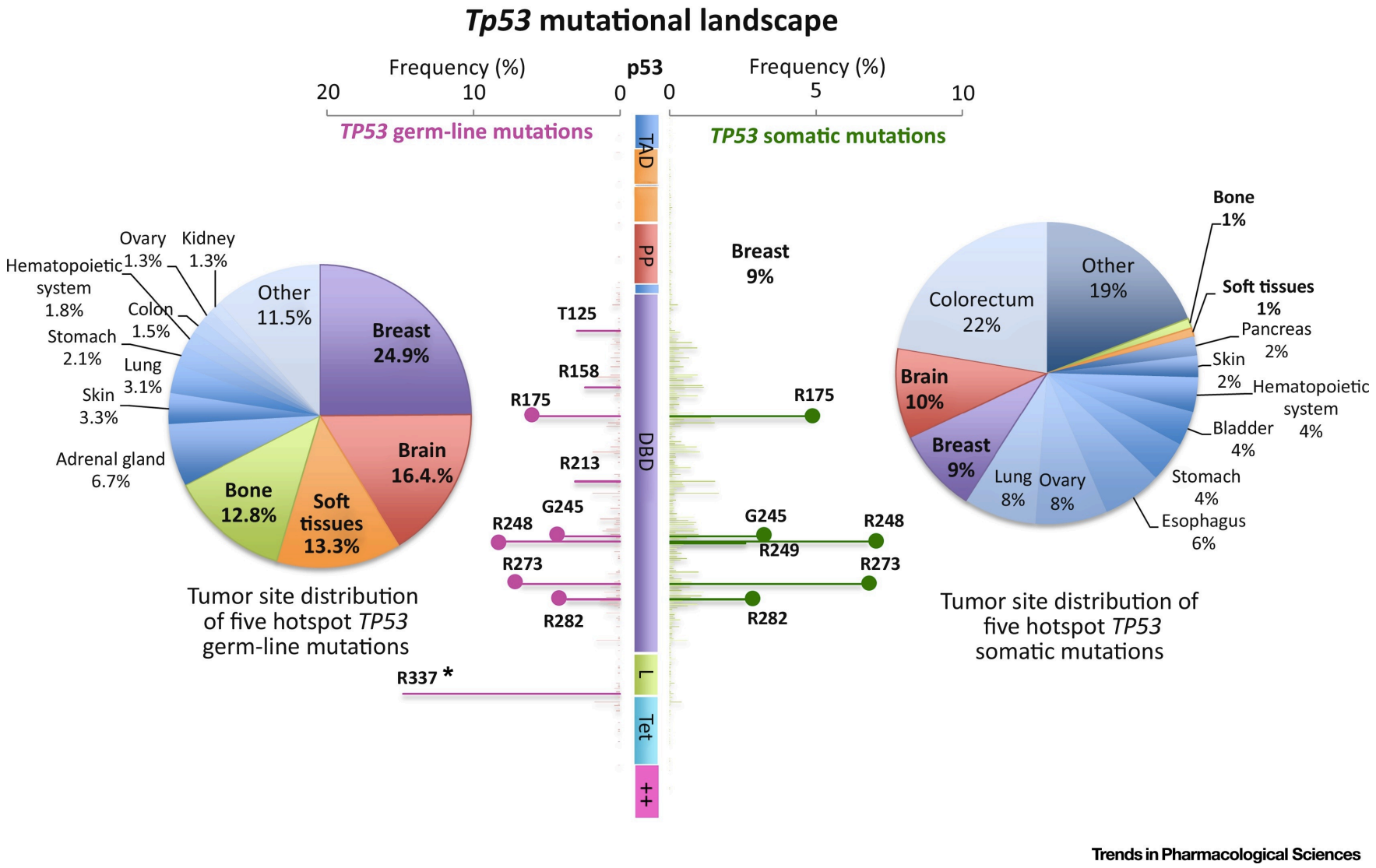


Joerger A.C. et al. PNAS, 2006

Tumour type	***TP53* mutation frequency (%)**	**Most common *TP53* mutations***
Ovarian serous carcinoma	94.6	R273H=Y220C>R248Q>R175H
Lung squamous cell carcinoma	79.3	R158L>R175G>V157F=R213X=T125T
Head and neck squamous cell carcinoma	69.8	R175H=R273H=R213X=R282W>R248W

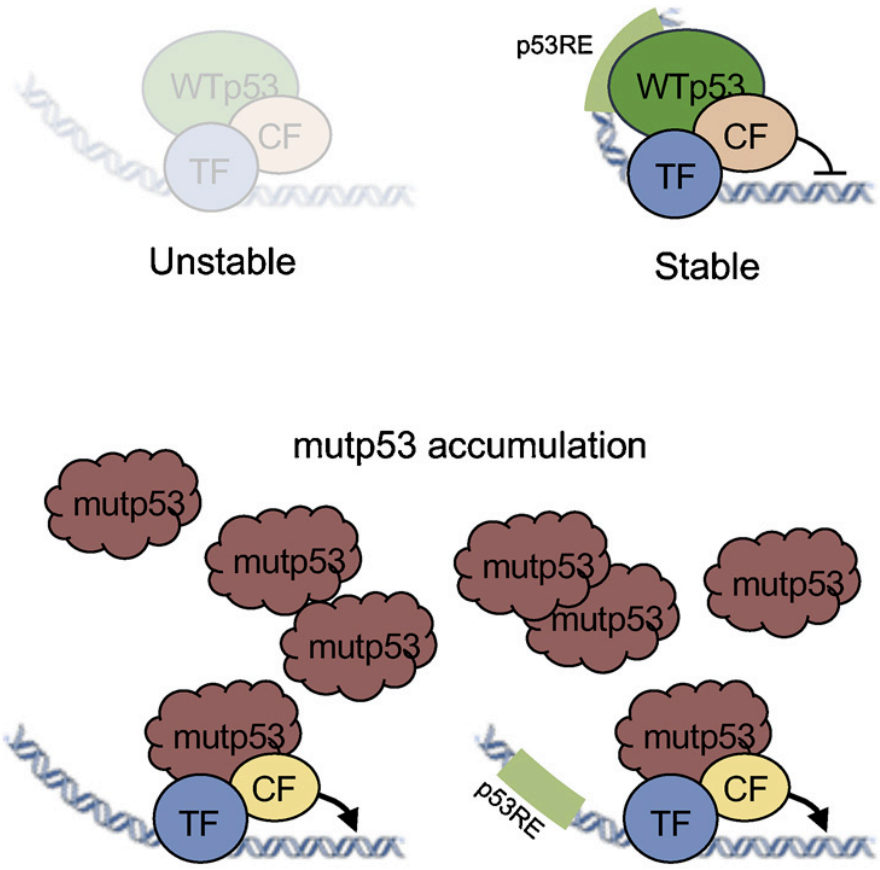
Bykov et al., Nat Rev Cancer, 2018

*TP*53 mutations in Li-Fraumeni Syndrome



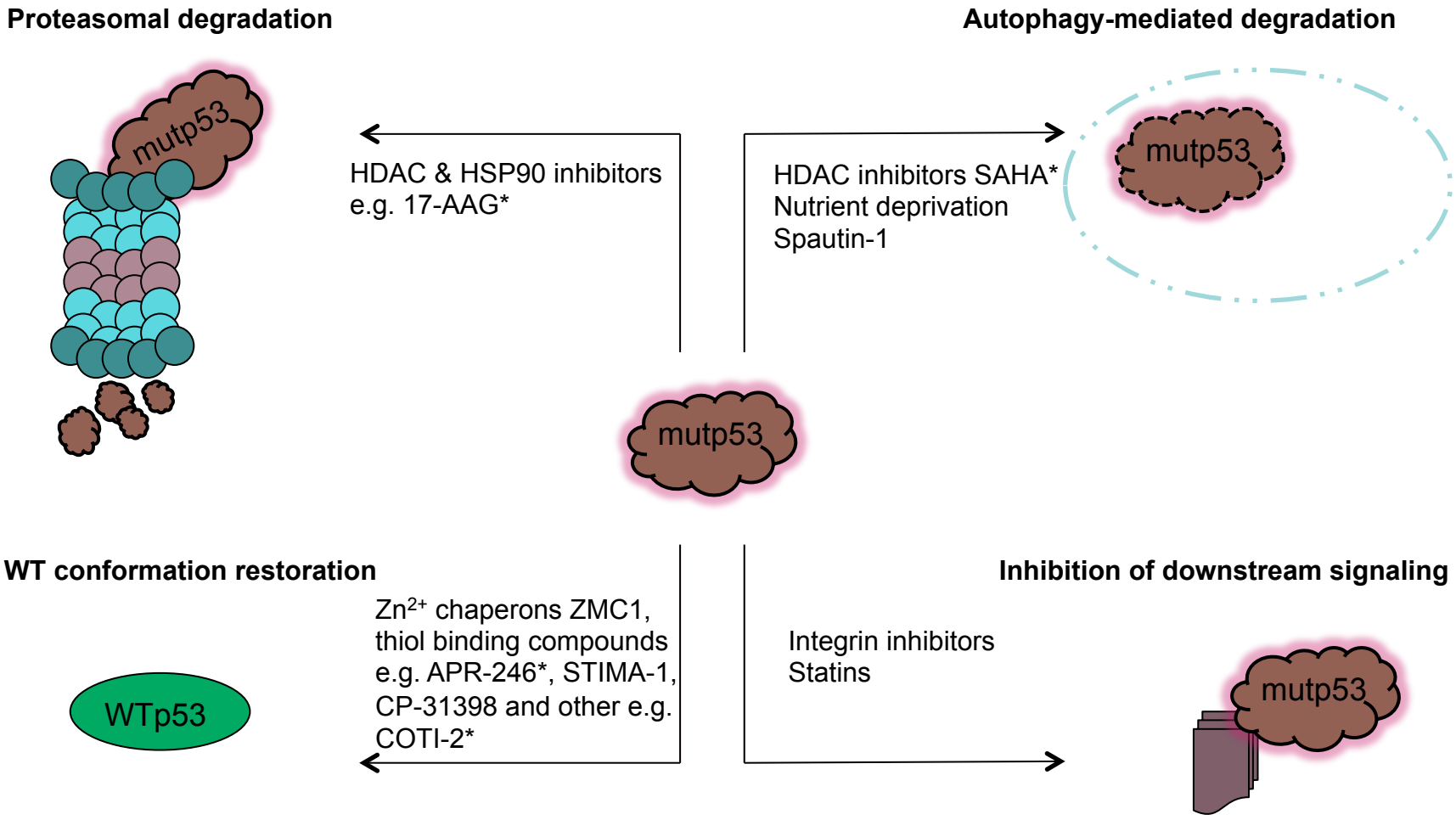
Zhou et al., Trends Pharmacol Sci, 2017

Mechanism of Gain-of-Function of mutp53



Adapted from Stiewe & Haran, Drug Resistance Update, 2018

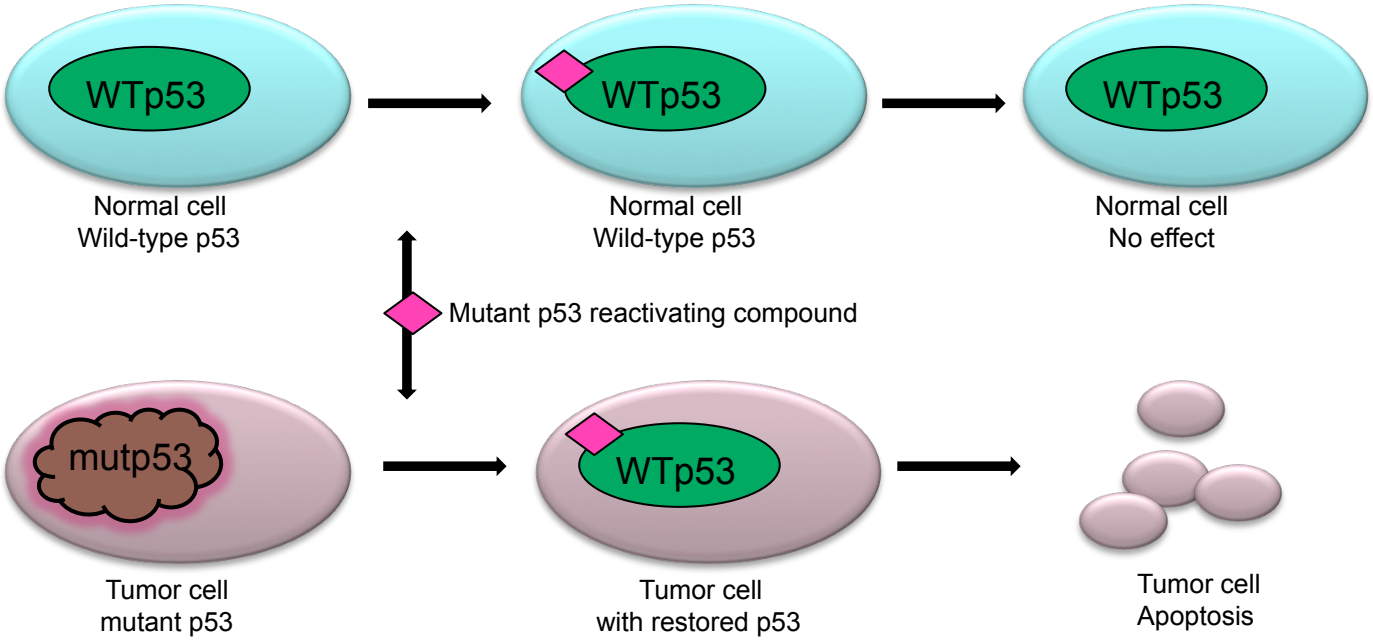
Approaches to target missense-type mutp53

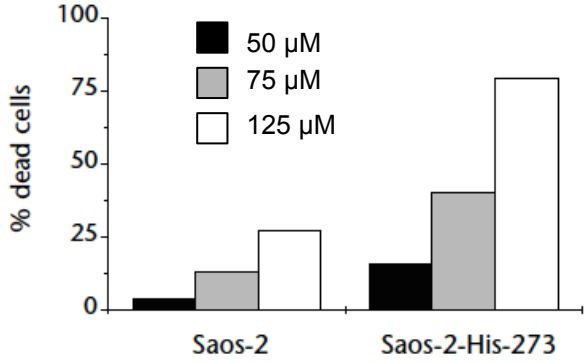


* In clinical development

Based on Green et al., Ann Oncol, 2018

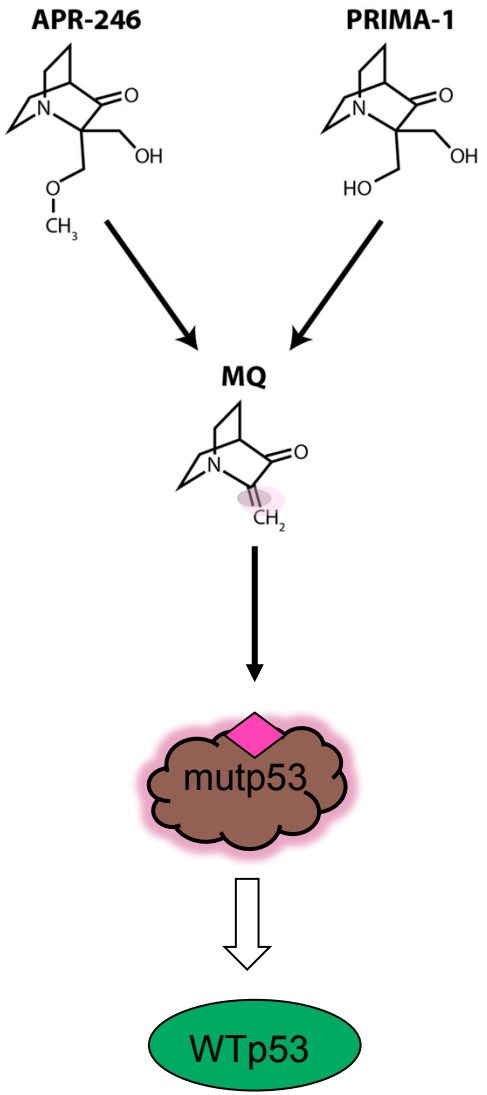
PRIMA-1 reactivates mutp53





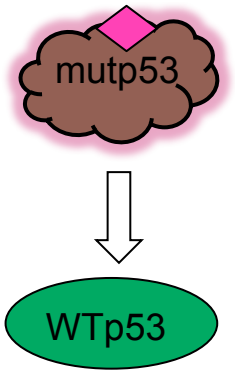
Bykov et al., Nat Med, 2002

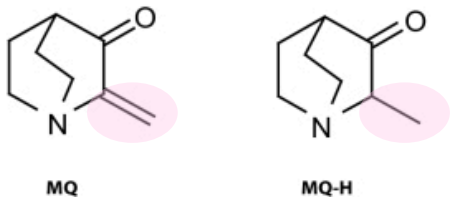
PRIMA-1 and APR-246 are converted to MQ

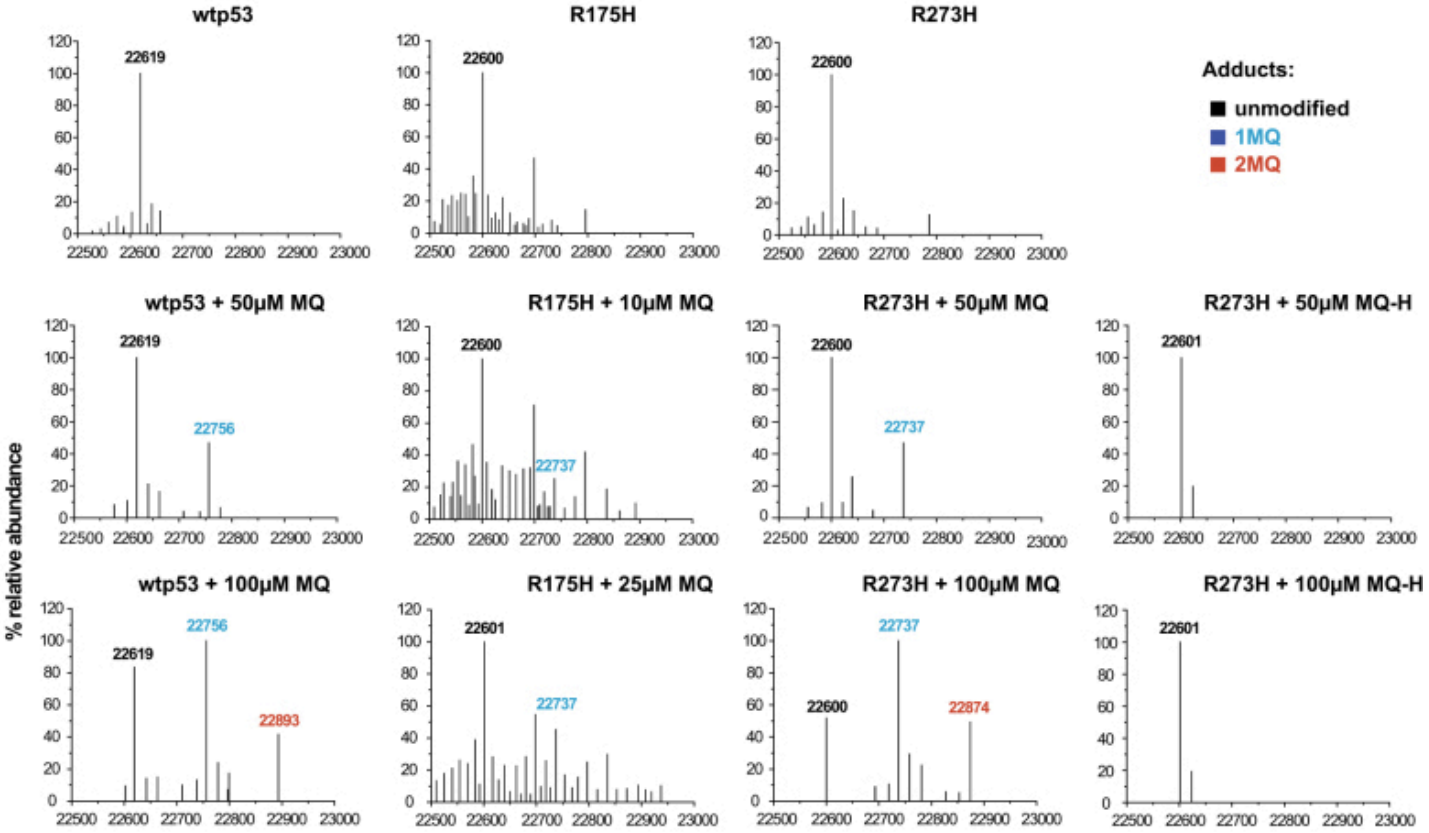


Adapted from Bykov et al., Front Oncol, 2016

MQ binds to cysteines in wild-type and mutp53

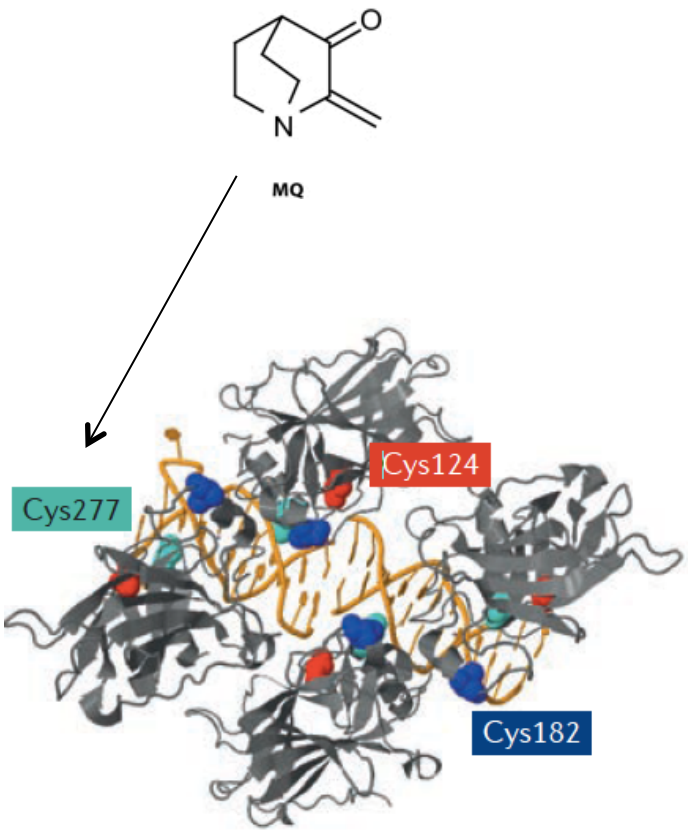


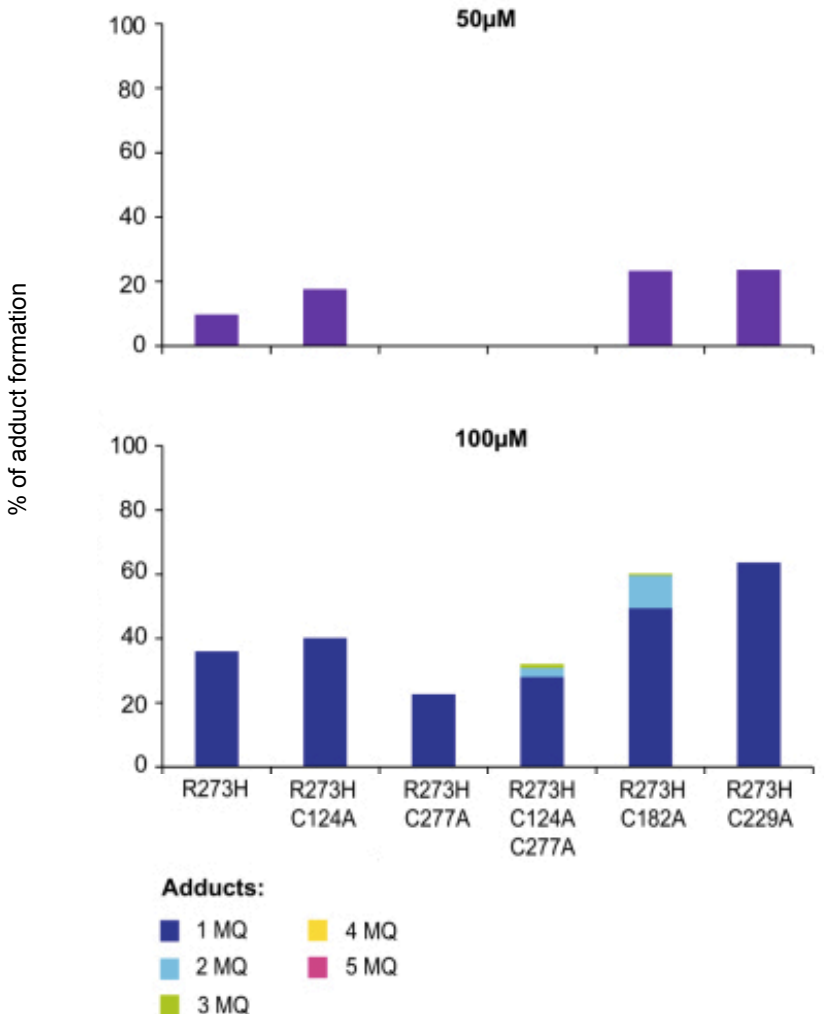




Zhang et al., CDDis, 2018

Cysteine 277 is a prime binding site of MQ in mutp53

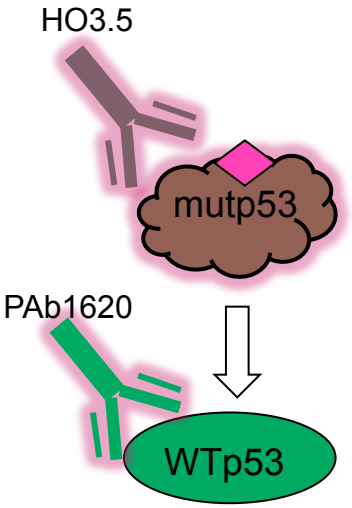


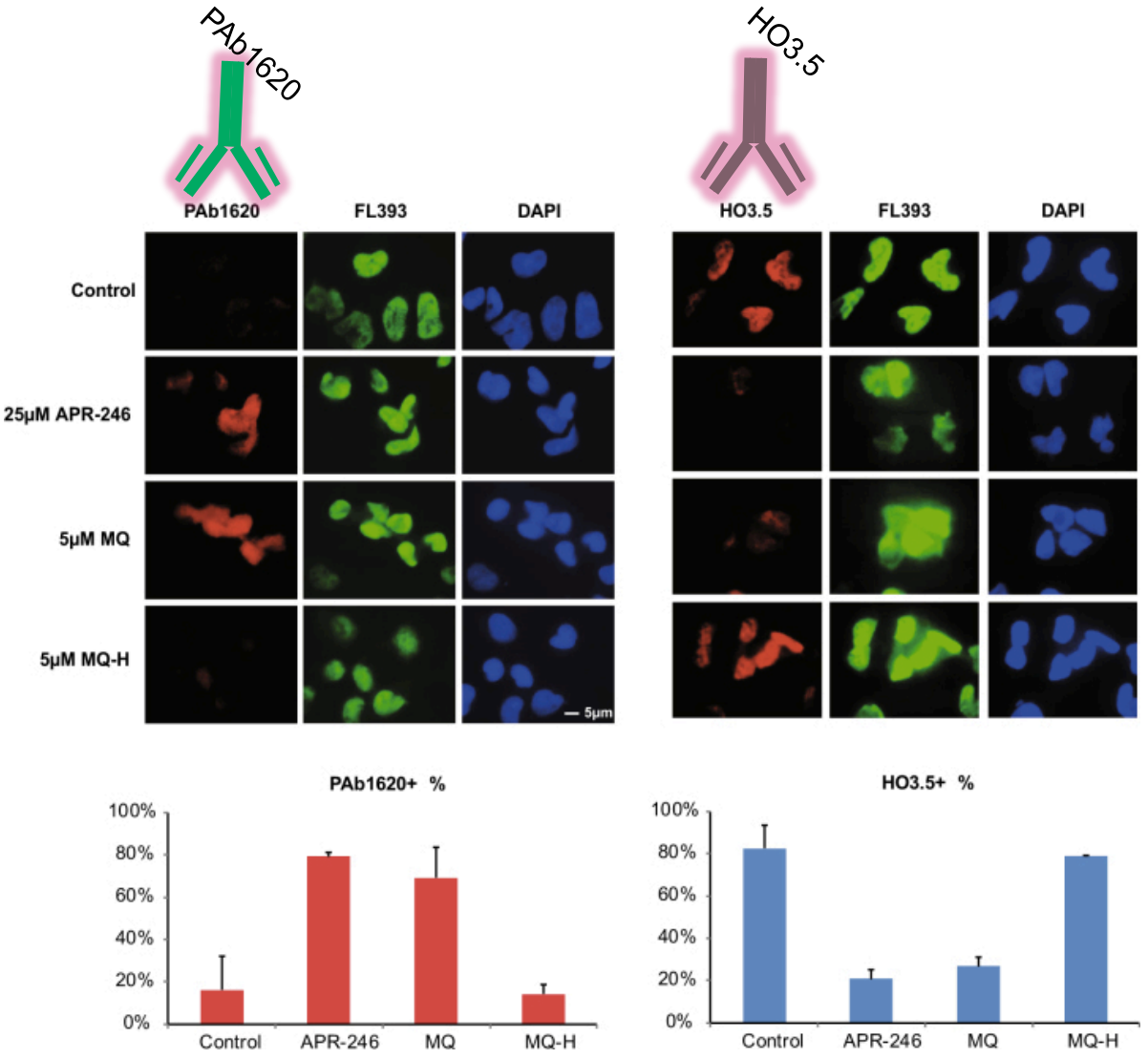


Adapted from Bykov et al., Nat Rev Cancer, 2018

Zhang et al., CDDis, 2018

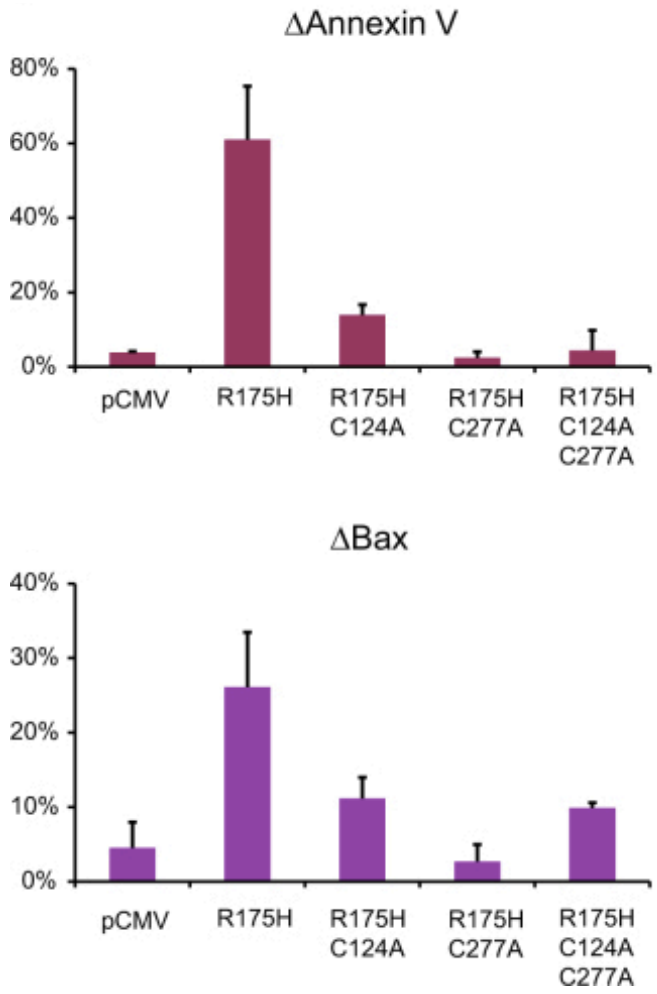
MQ restores WTp53 epitope in R175Hmutp53 ovarian cancer cells

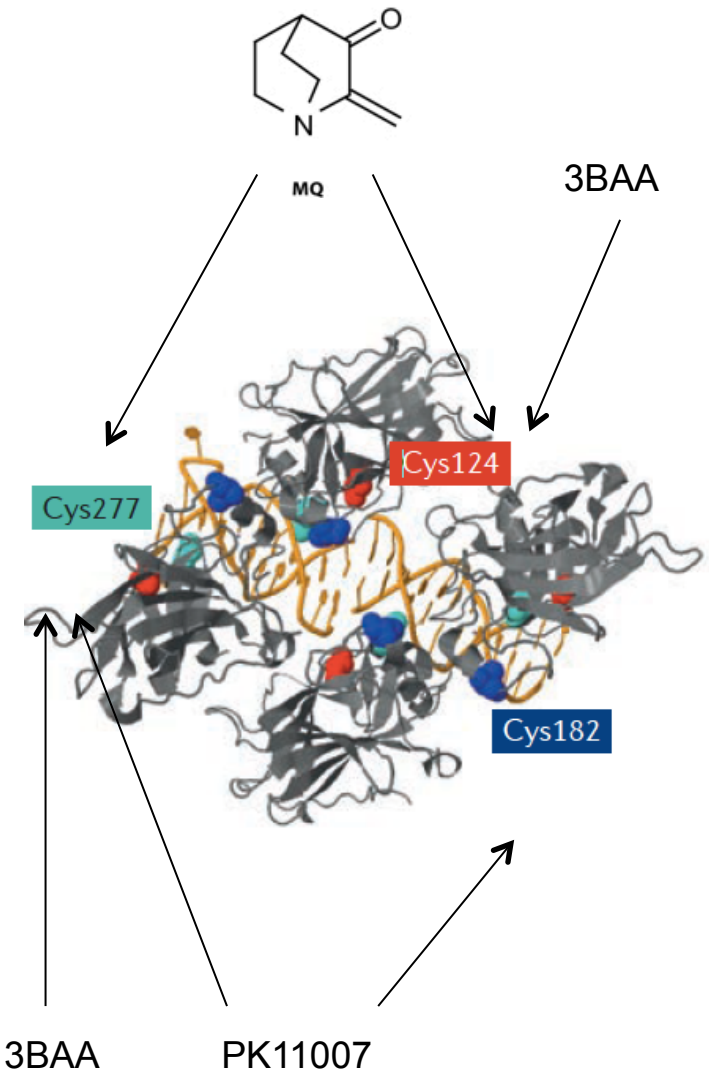




Zhang et al., CDDis, 2018

Cys124 and Cys277 are crucial for APR-246/MQ-mediated R175H-mutp53 reactivation in cancer cells





Zhang et al., CDDis, 2018

Adapted from Bykov et al., Nat Rev Cancer, 2018

Targeting p53 *in vivo*: first-in-human clinical study with APR-246 in refractory hematologic malignancies

An Open-label Phase I Dose Escalating Study of APR-246 for Infusion in Patients With Refractory Hematologic Malignancies or Prostate Carcinoma

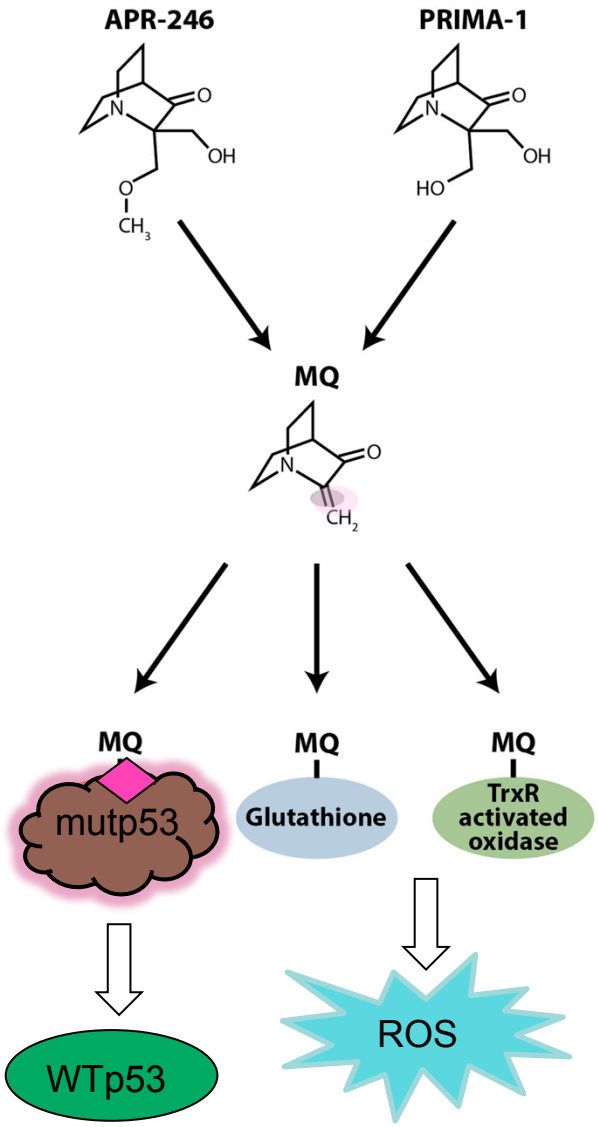
- Phase I – completed
- Outcome: maximum tolerated dose (MTD), dose limiting toxicities (DLT) and pharmakokinetics (PK)
- Enrolled: 22 participants (incl. 7 AML, 7 prostate cancer)

Results:

- 2 hrs IV infusion 2 – 90 mg/kg for 4 constitutive days
- MTD 60 mg/kg
- DLT: ALT/AST n=1; dizziness, fatigue, sensory disturbances n=2
- Tumor cells from some patients showed induction of apoptosis and p53 target genes
- One patient with AML with mutp53 showed a reduction of blast from 46% to 26%

Lehmann et al., J Clin Oncol, 2012

MQ reacts with p53, glutathione and TrxR



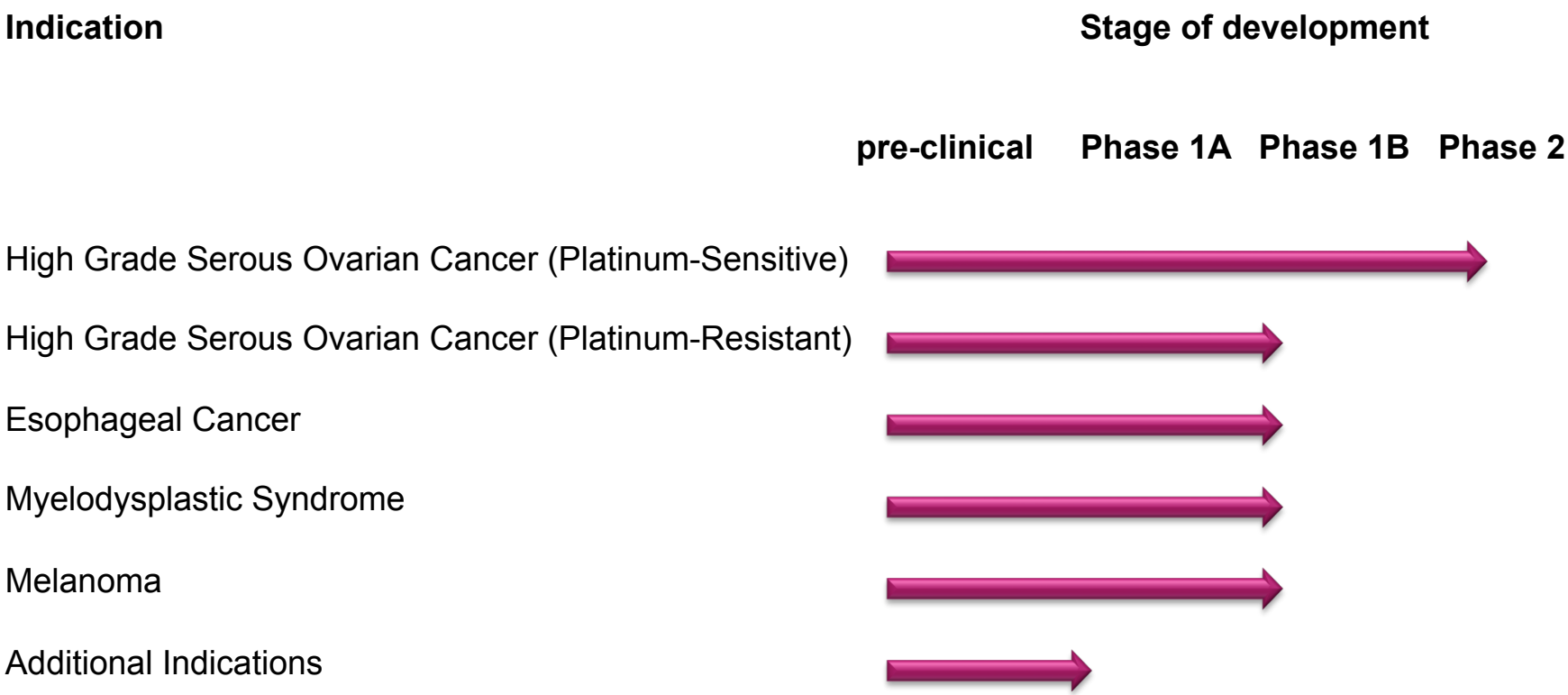
Adapted from Bykov et al., Front Oncol, 2016

Examples of mutant p53-directed clinical trials

Drug	Sponsor	Mechanism	Phase	Tumor	No	Status	NCT
APR-246	Aprea Therapeutics AB	Conformation restoration, nucleophilic addition, reactivity with free thiols	I	Hematology and prostatic neoplasms	36	completed	00900614
APR-246 with Dabrafenib	Aprea Therapeutics AB		Ib/II	melanoma	31	recruting	03391050
***APR-246 with PLD**	Aprea Therapeutics AB		II	Platinum resistant high-grade Serous Ovarian Cancer	25	recruting	03268382
APR-246 with azacitidine	H. Le Moffitt Cancer Center and Aprea Therapeutics AB		Ib/II	TP53 mutant myeloid neoplasm	60	recruting	03072043
APR-246 with carboplatin and PLD	Aprea Therapeutics AB		Ib/II	Platinum sensitive high-grade Serous Ovarian Cancer	400	recruting	02098343
APR-246 with azacitidine	Groupe Francophone des Myelodysplasies and Aprea Therapeutics AB		Ib/II	TP53 mutant myeloid neoplasm	20	Not recruting yet	03588078
APR-246 with 5-FU	Peter MacCallum Cancer Centre and Aprea Therapeutics AB		Ib/II	Oesophageal Carcinoma	38	recruting	02999893
COTI-2	Critical Outcomes Technologies	Conformation restoration and inhibition of PI3K	I	Gynaecological cancers and HNSCC	56	recruting	02433626
Ganetespib	Sarcoma Alliance for Research through Collaboration	HSP90 inhibitor	I/II	Malignant Peripheral Nerve Sheath Tumors (MPNST); sarcoma	20	completed	02008877
Ganetespib with Fulvestrant	Dana-Farber Cancer Institute		II	HR+ Breast Cancer	50	Active, not recruting	01560416
Ganetespib with capecitabine	Emory University		I	Rectal cancer	16	completed	01554969
Kevetrin	Cellceutix Corporation	Ser15 phosphorylation	I	Solid tumors	48	completed	01664000

From www.clinicaltrials.gov
* Trial in UK

Overview of on-going clinical trials with APR-246 in combination with the existing treatments



From www.aprea.com

Clinical trials in platinum-resistant (PiSARRO-R) and platinum-sensitive recurrent High Grade Serous Ovarian Cancer

1. **PiSARRO-R:** p53 Suppressor Activation in Platinum-Resistant High Grade Serous Ovarian Cancer, a Phase II Study of Systemic Pegylated Liposomal Doxorubicin Chemotherapy With APR-246

- Arm: Experimental: Phase II: APR-246 (IV) + PLD (IV)
- Estimated: 25 participants
- ORR - 18 months; efficacy according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1)

2. p53 Suppressor Activation in Recurrent High Grade Serous Ovarian Cancer, a Phase Ib/II Study of Systemic Carboplatin Combination Chemotherapy With or Without APR-246

- Arm: Experimental: Phase Ib: APR-246 (IV) dose escalation + Carboplatin/PLD – DLT/AEs/Cmax/AUC
- Arm: Experimental: Phase II: Arm A: APR-246 + Carboplatin/PLD
- Arm: Active comparator: Phase II: Arm B: Carboplatin/PLD – PFS/OS/ORR 24 months
- Estimated: 400 participants

Results of clinical studies with APR-246

P53 suppressor Activation in Recurrent High-Grade Serous Ovarian Cancer, a Phase Ib/II Study of Systemic Carboplatin and pegylated liposomal doxorubicin (PLD)

1. The median progression free survival (PFS) for 22 evaluable patients, as measured by Response Evaluation Criteria in Solid Tumors (RECIST) or GCIG, was 316 days (95% CI, 280-414 days).

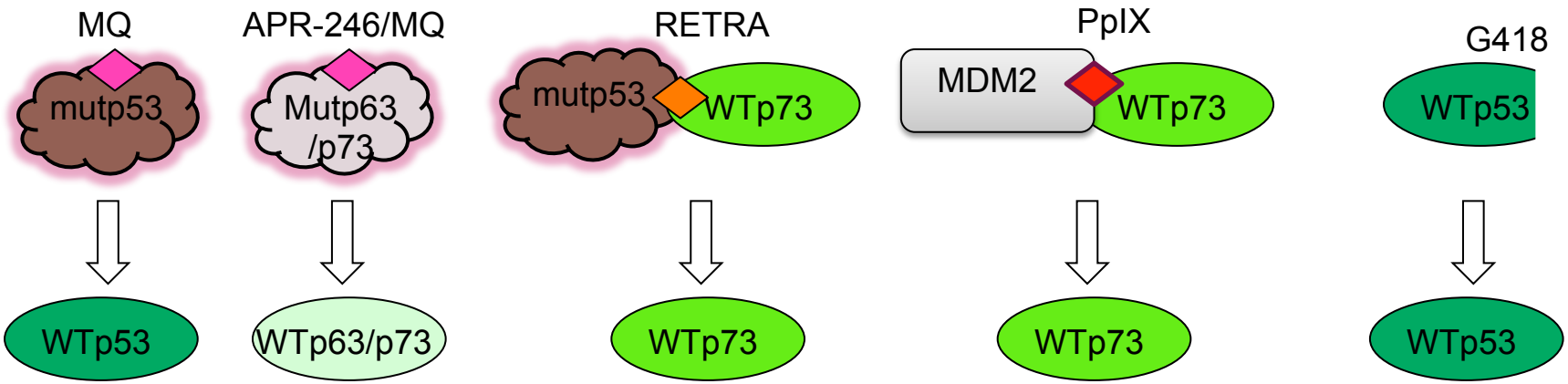
2. Of 22 patients with radiologically measurable lesions, 3 had confirmed complete response, 10 had confirmed partial response, 8 had stable disease and 1 was not evaluable. (www.aprea.com)

Phase I/IIb safety and Efficacy of APR-246 w/Azacitidine for the treatment of TP53 Mutant Myeloid Neoplasm

1. Overall Response Rate (ORR) (by IWG) of 100% in all evaluable patients: 8 complete response (CR) (89%) and 1 marrow Complete Response (mCR) (11%).

2. No treatment-related serious adverse events or dose-limiting toxicities to date. (Aprea Therapeutics AB, poster communication, EHA Meeting, Stockholm, 2018)

Other therapeutic approaches to target mutp53 tumors – reactivation of p53 ‘cousins’ p73 and p63



Acknowledgement

Collaboration

Karolinska Institutet
Department of Oncology-Pathology
Cancer Center Karolinska (CCK),
Prof. Klas Wiman,
Vladimir Bykov, PhD
Qiang Zhang, PhD

Funding
Stockholms Läns Landsting
SFO – Strategic Research Programe in Cancer; Karolinska Institutet
Åke Wibergs Stiftelse