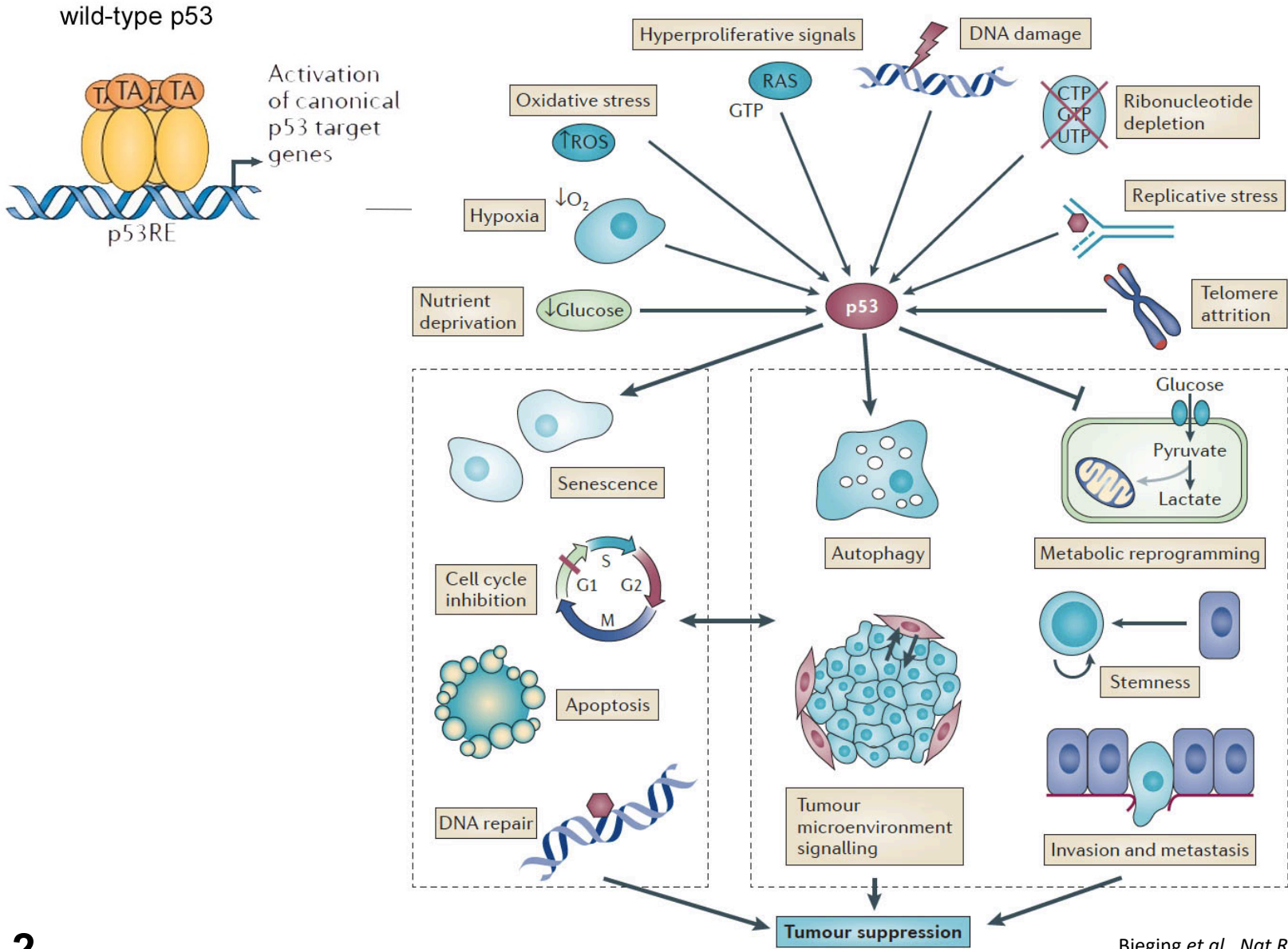


Corso di Oncologia Molecolare

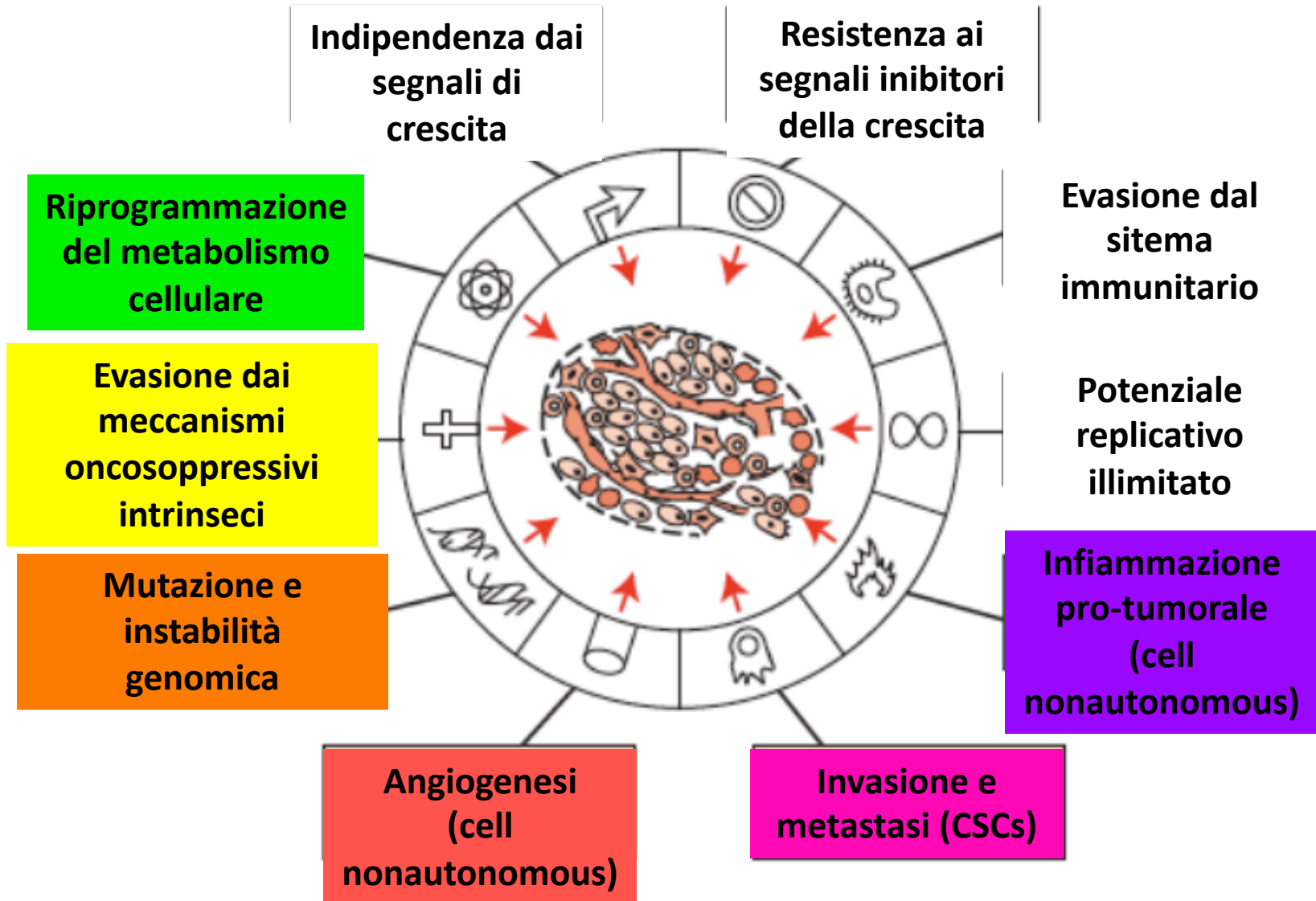
AA 2019-2020

Alterazioni della pathway di p53 nei tumori

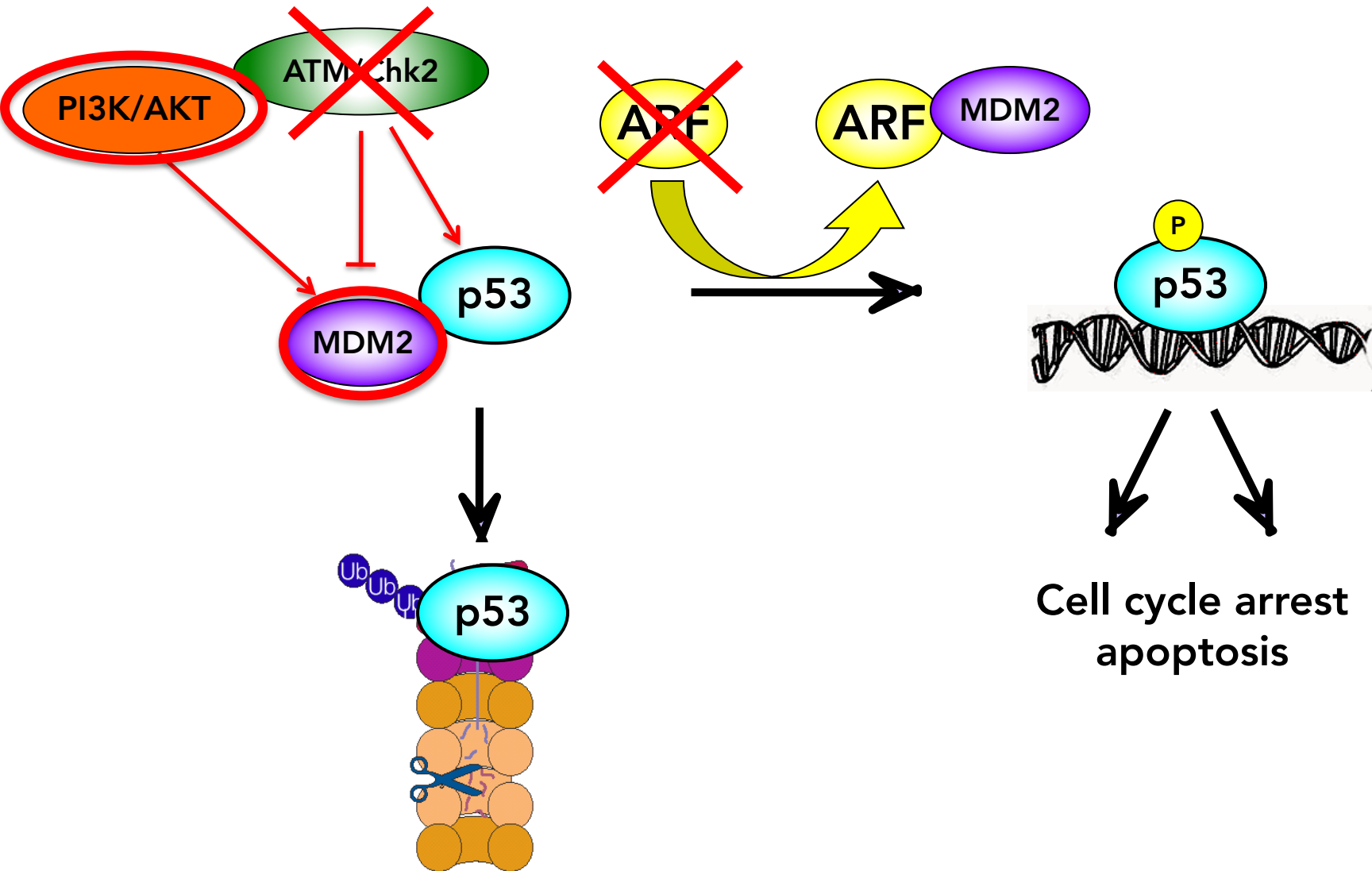
p53 induce diverse risposte cellulari oncosoppressive...



Quindi l'inattivazione di p53 facilita l'acquisizione di diversi hallmarks tumorali



Alterazioni della pathway in tumori che mantengono *TP53* wild-type



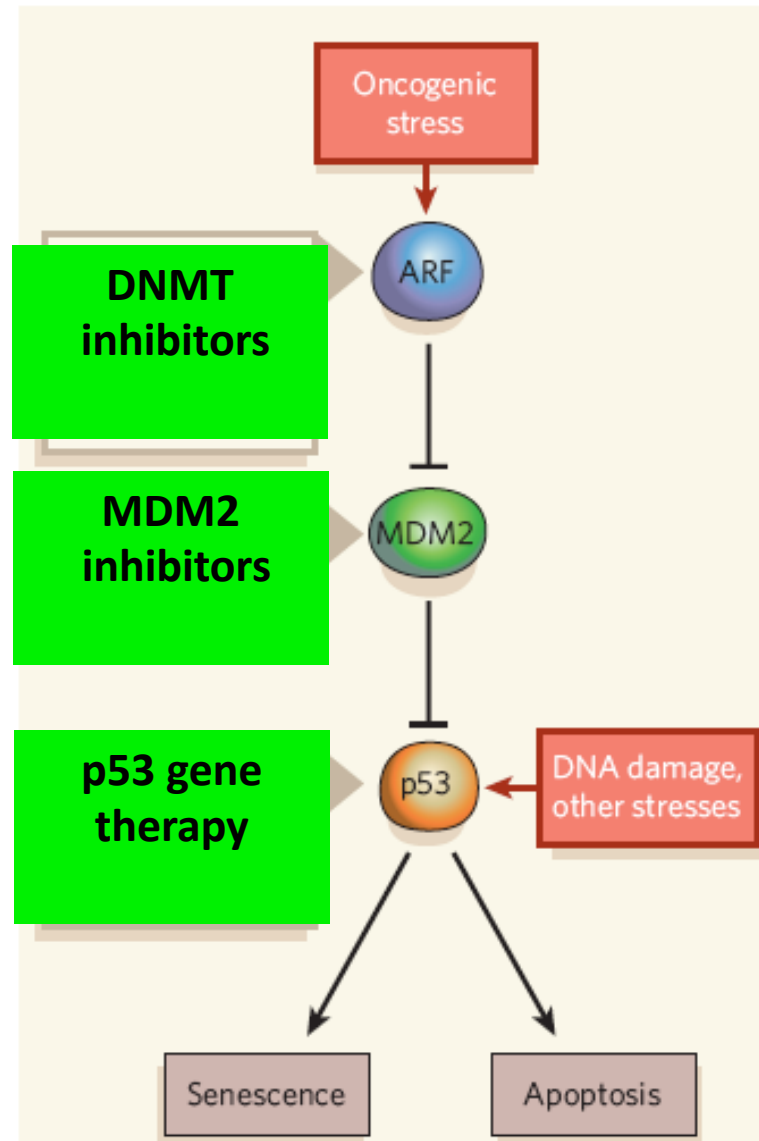
Strategie terapeutiche per la riattivazione della pathway in tumori che mantengono *TP53* wild-type

Work with mice revealed that persistent inactivation of the p53 tumor suppressor pathway is required for tumor maintenance

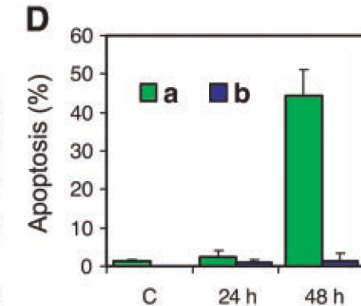
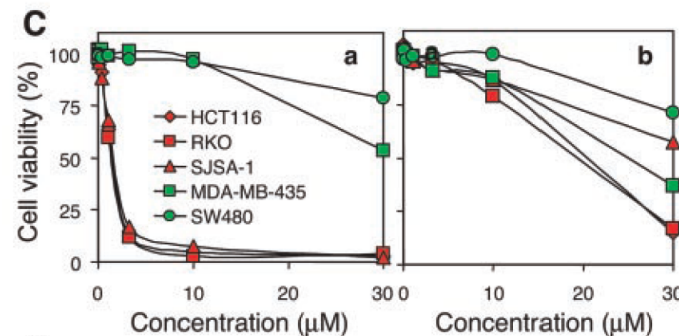
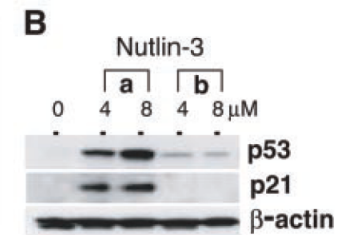
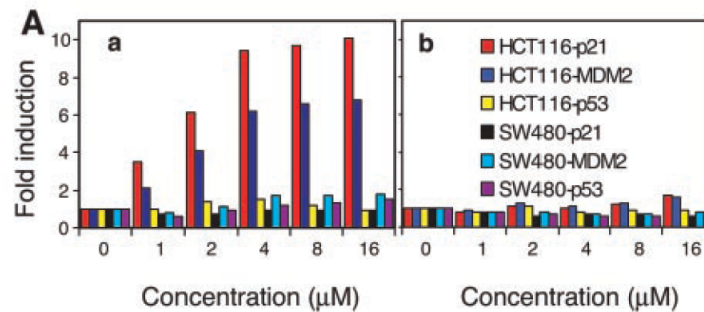
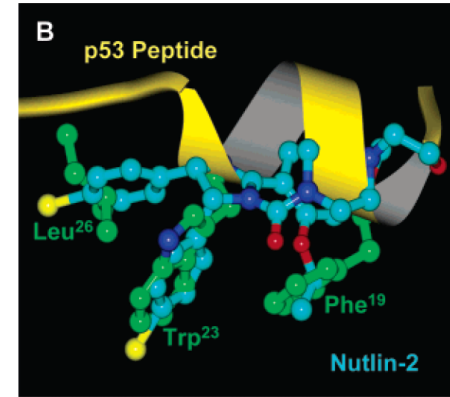
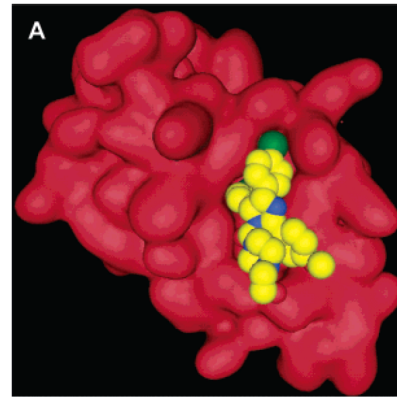
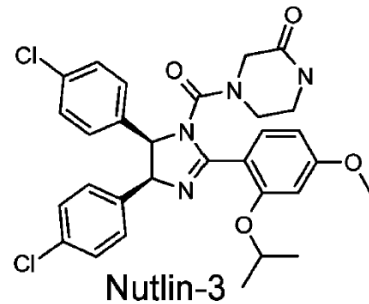
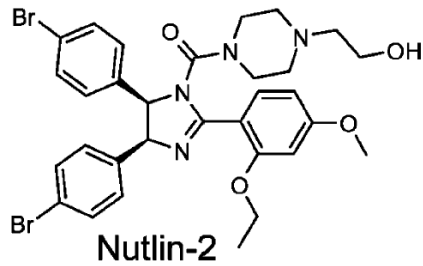
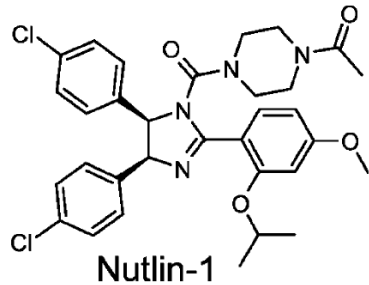
Reactivation of dormant p53 pathway leads to rapid regression of tumors in vivo

**through either
Apoptosis or
Senescence**

Strategie terapeutiche per la riattivazione della pathway in tumori che mantengono *TP53* wild-type

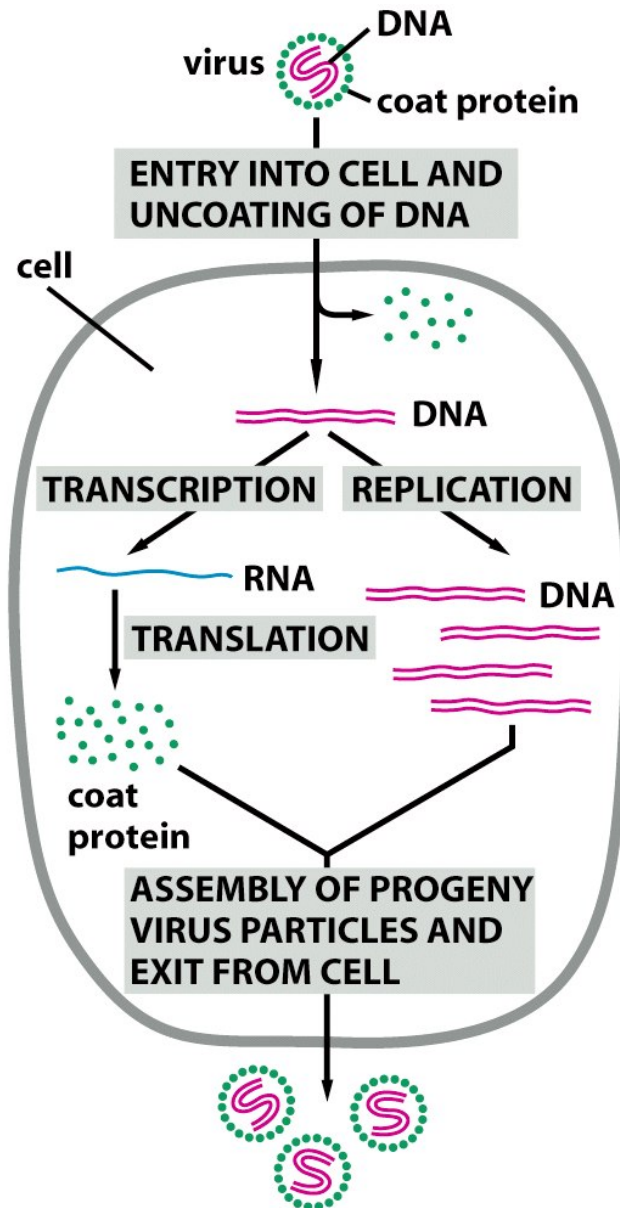


Le NUTLINE inibiscono l'interazione di MDM2 con p53

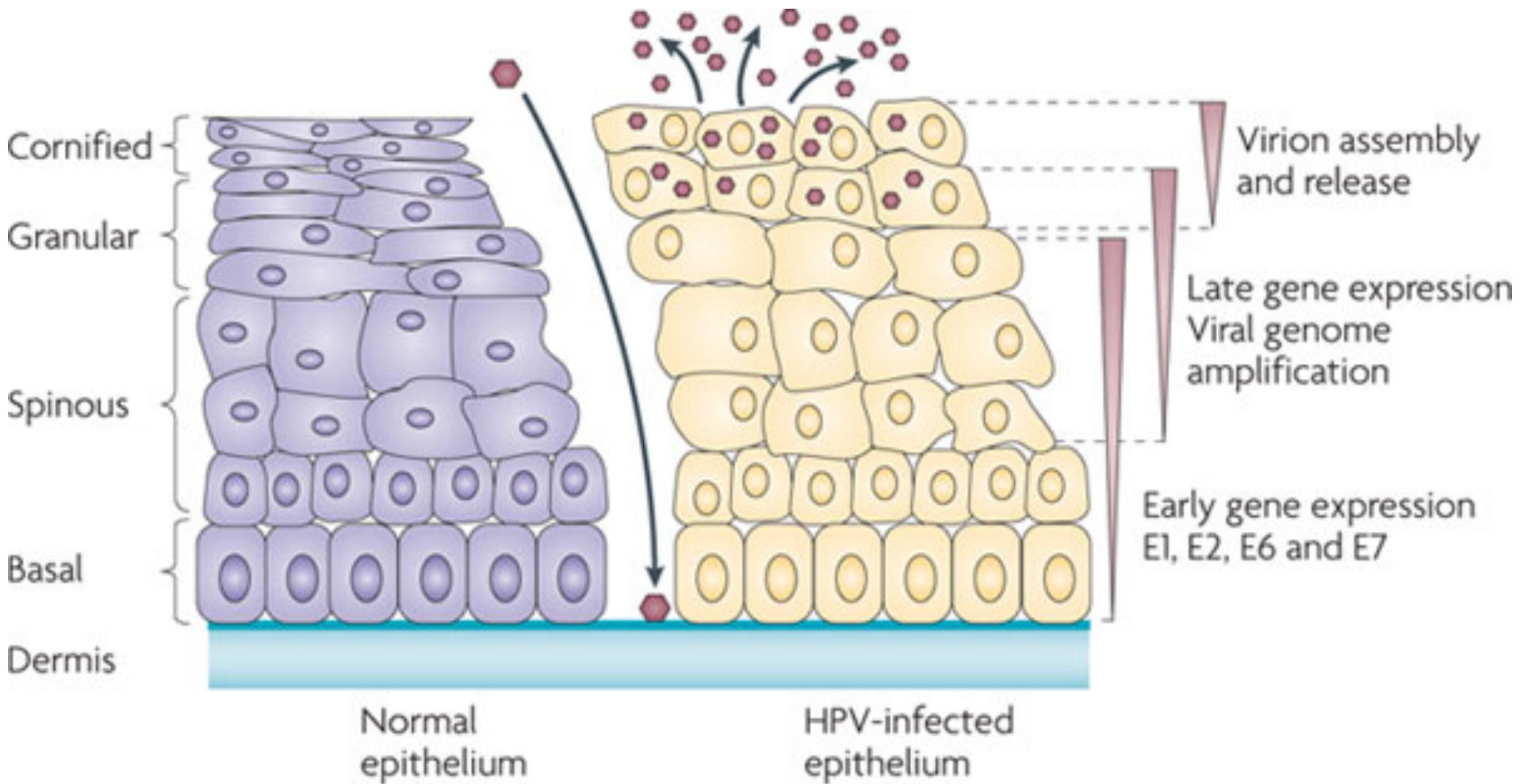


I piccoli virus oncogeni a DNA inibiscono le pathways di RB e p53

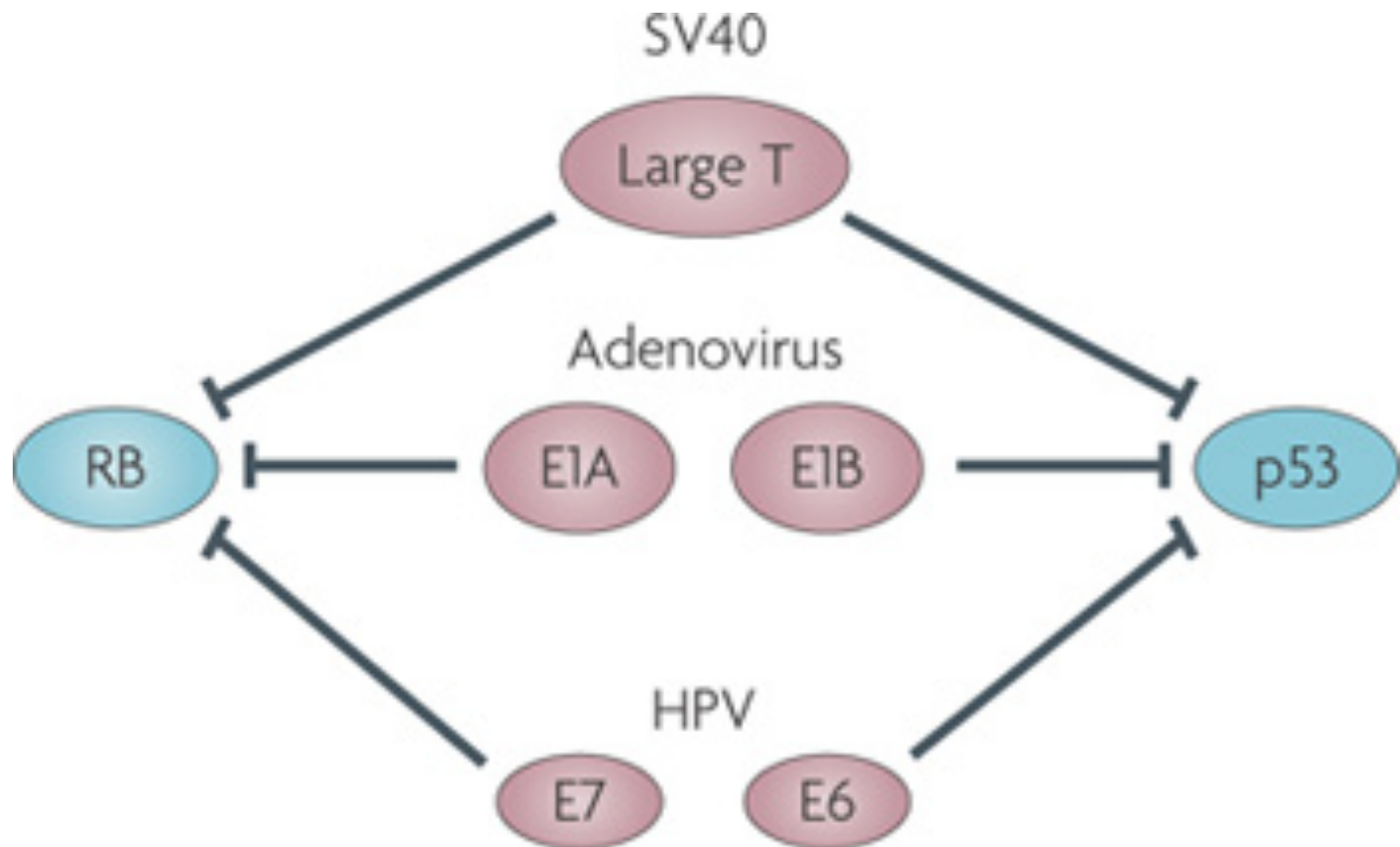
Ciclo vitale dei DNA tumor viruses



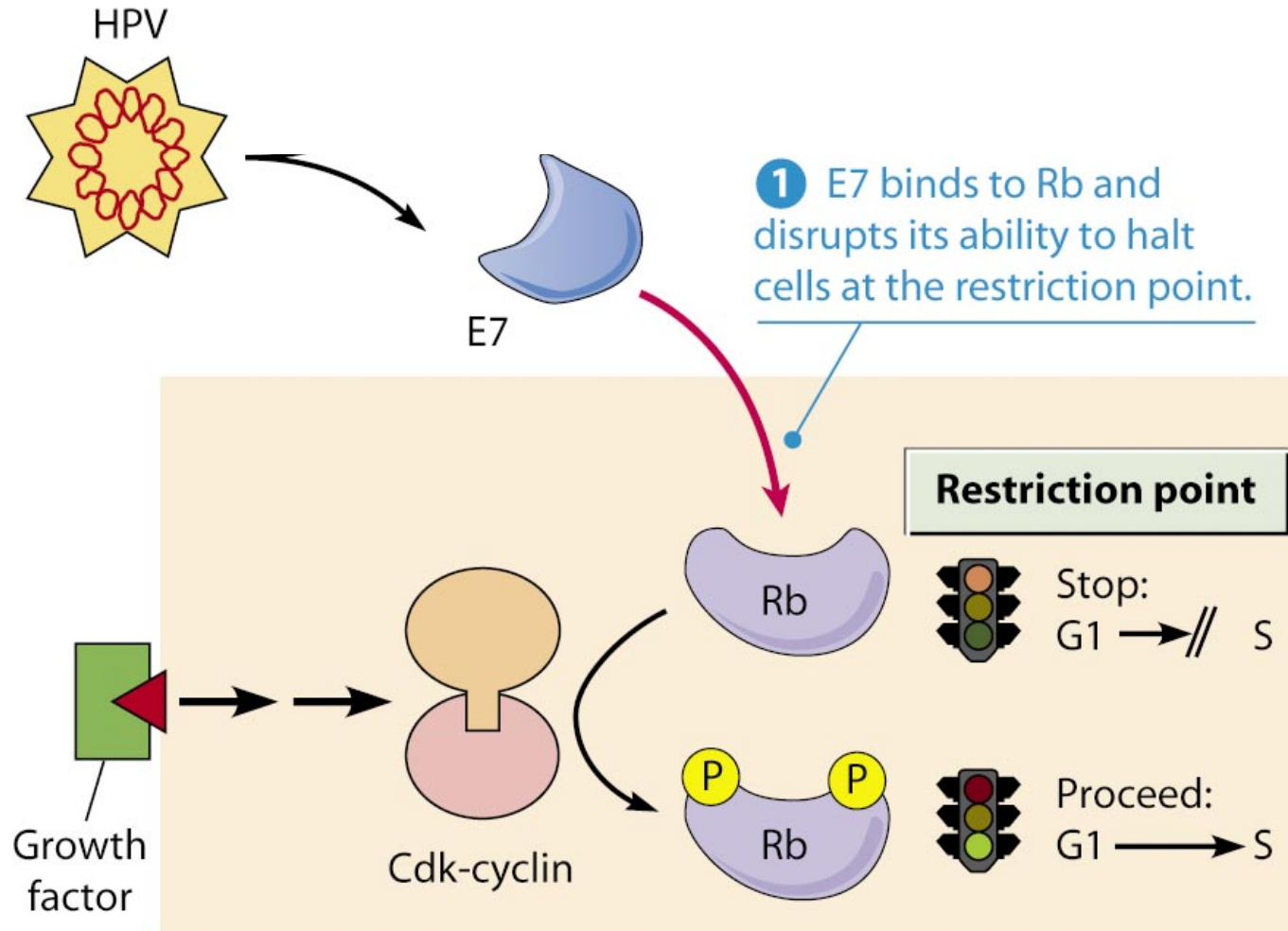
Ciclo vitale dei papillomavirus (HPV)



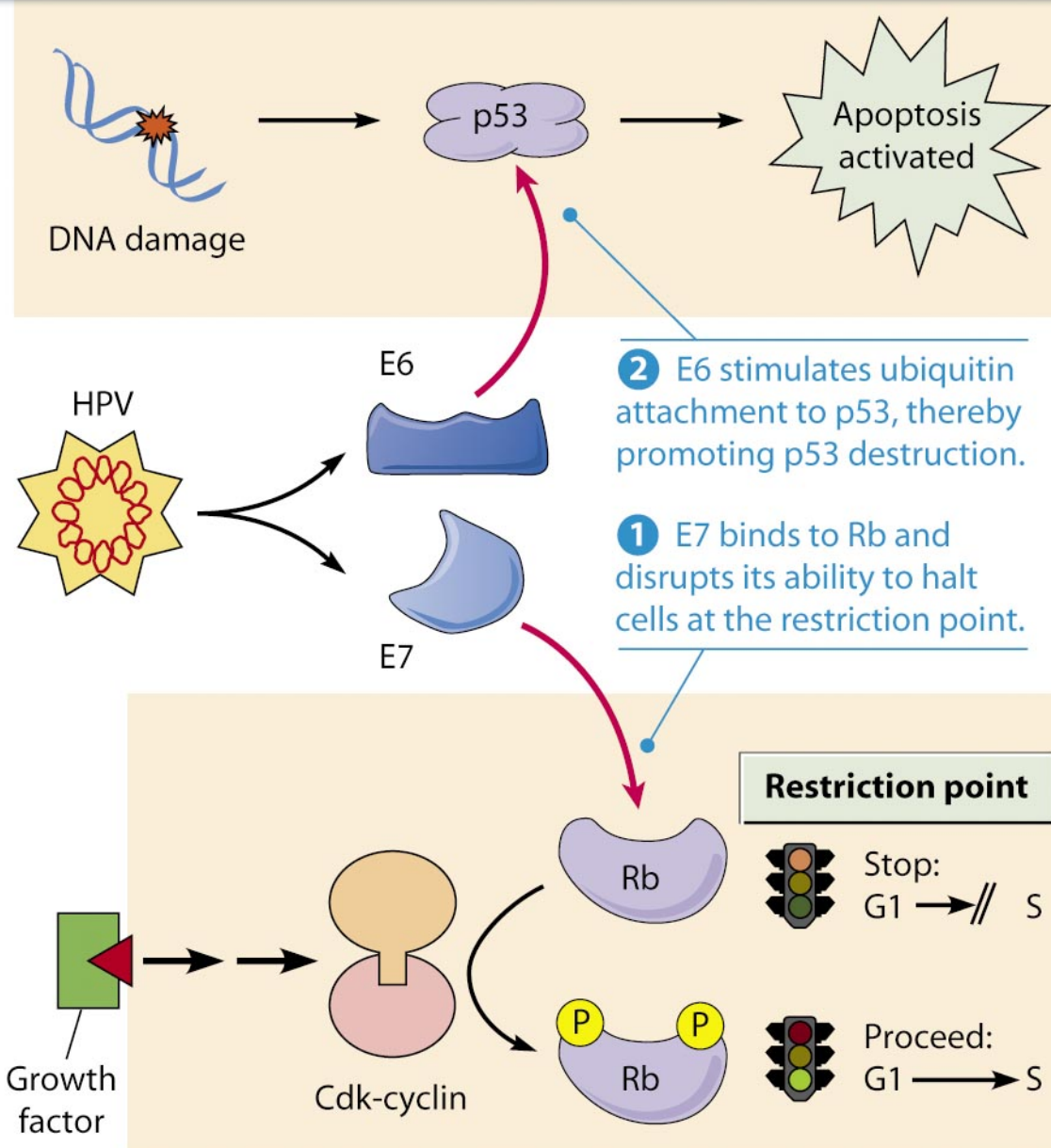
Il potenziale oncogenico dei piccoli virus a DNA dipende da oncoproteine che inibiscono RB e p53, i fattori di competenza virale



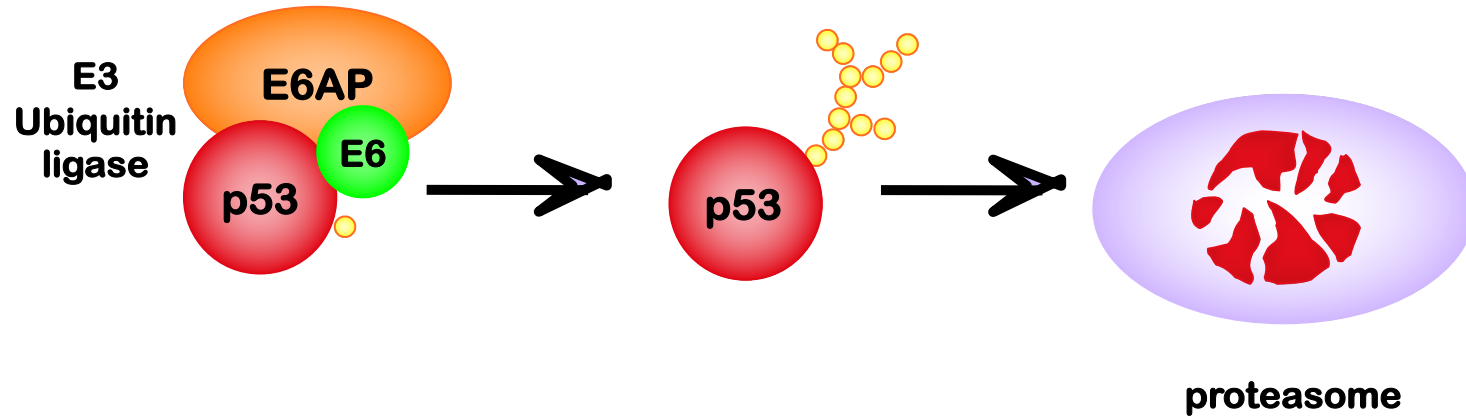
HPV E6 e E7 sono fattori di competenza



HPV E6 and E7 sono fattori di competenza



Lo stress cellulare non blocca la degradazione di p53 indotta da E6



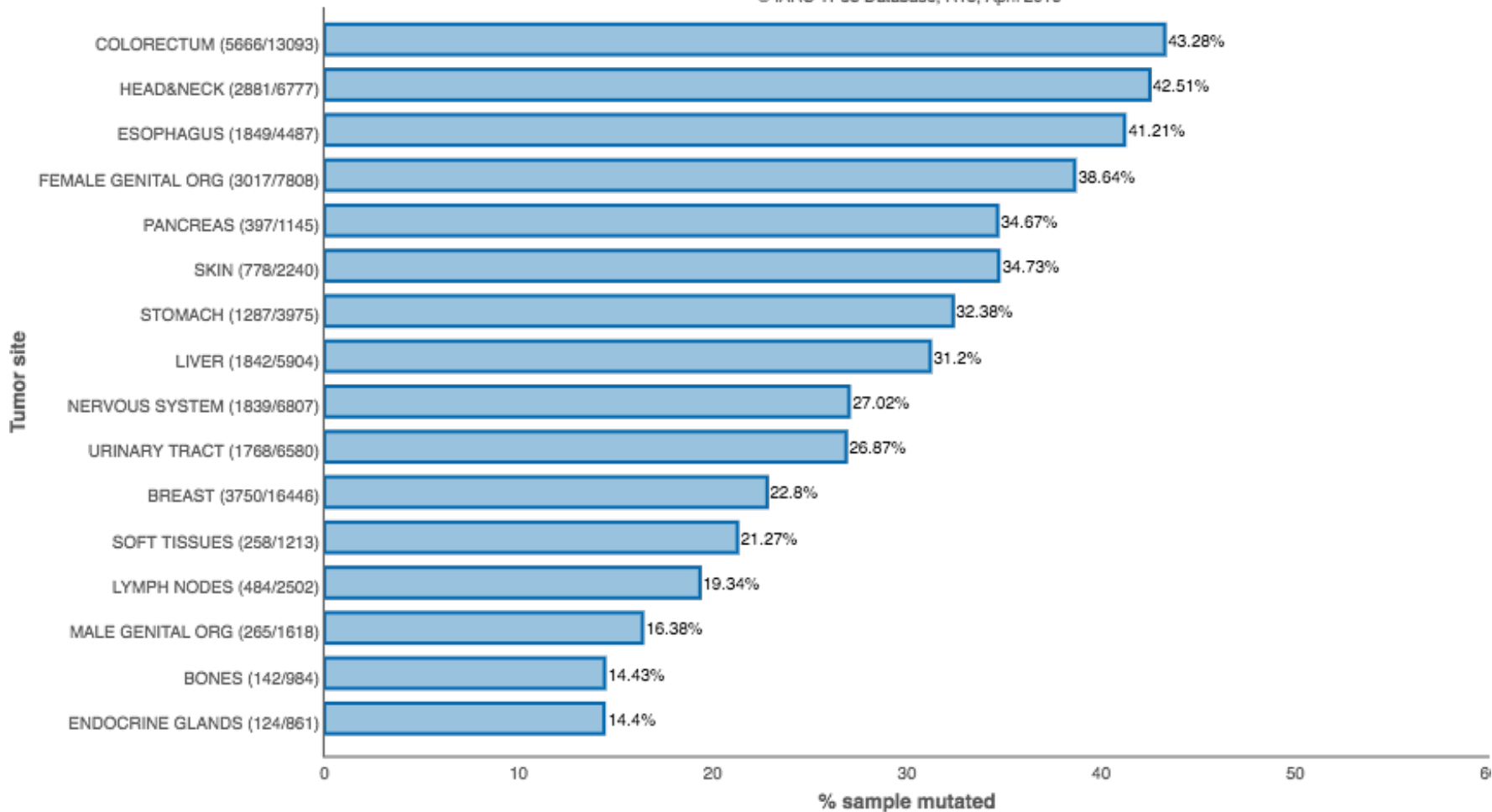
La strategia più efficace per i tumori associati a infezione da HPV è la prevenzione



TP53 è il gene più frequentemente mutato nei tumori

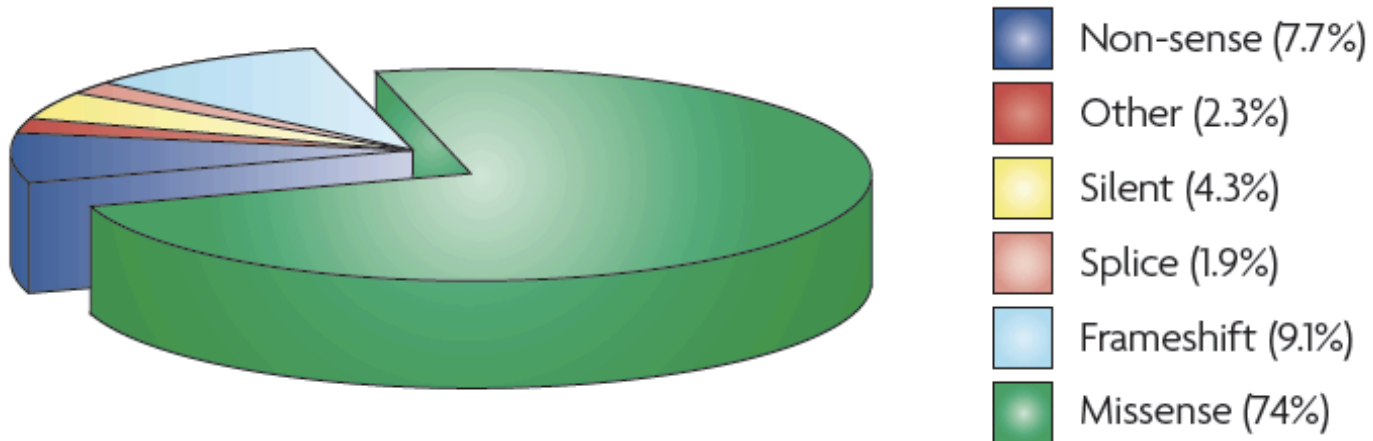
Mutation Prevalence (N = 26347)

© IARC TP53 Database, R18, April 2016

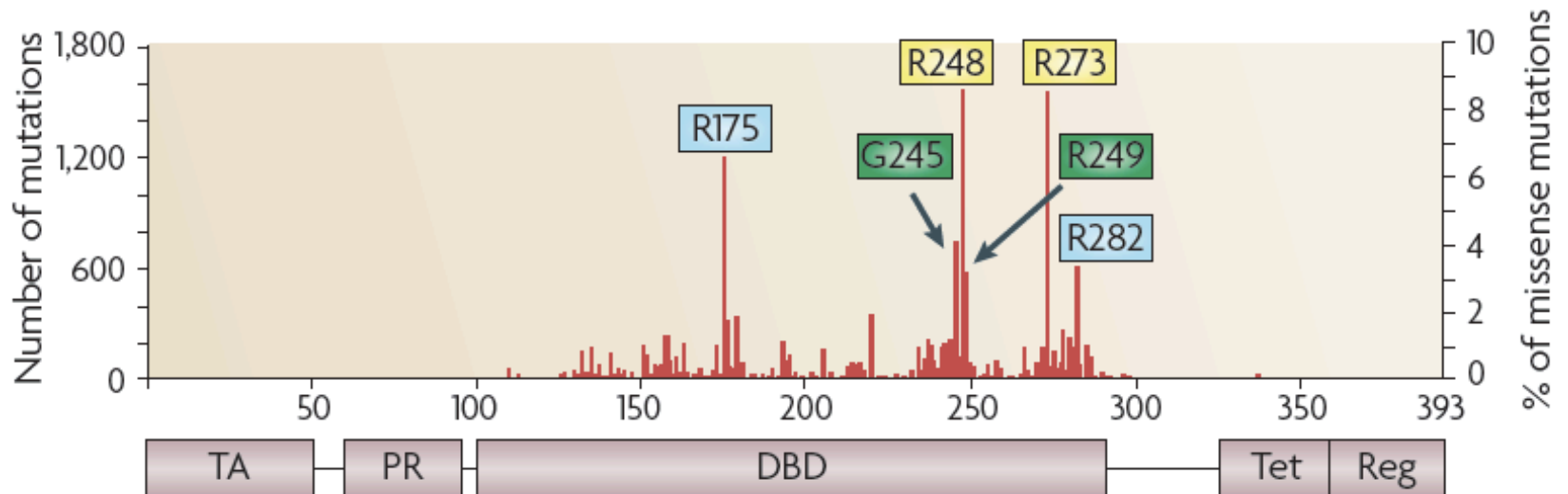


TP53 ha un pattern mutazionale peculiare

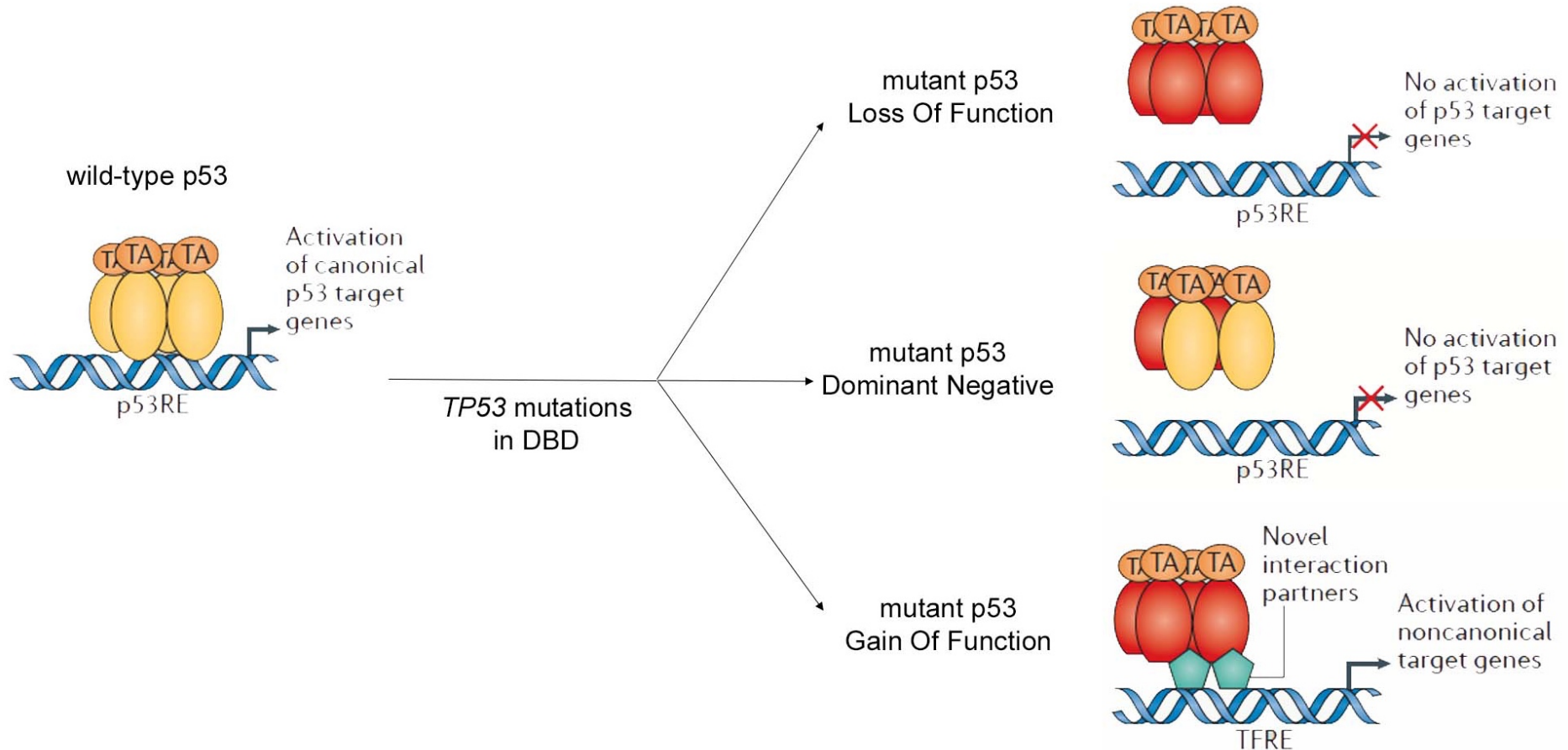
a



b

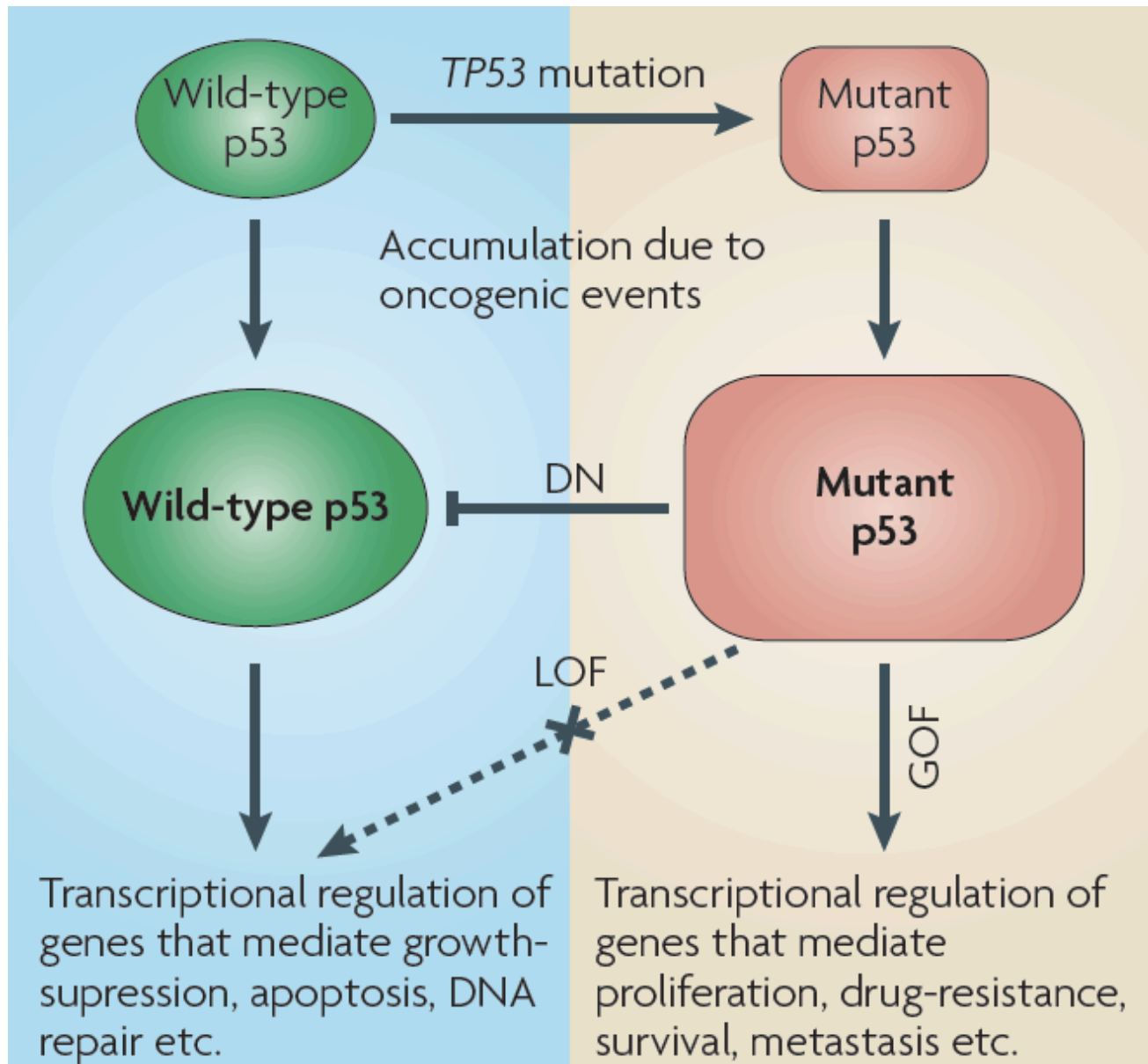


Conseguenze funzionali delle mutazioni missenso di TP53

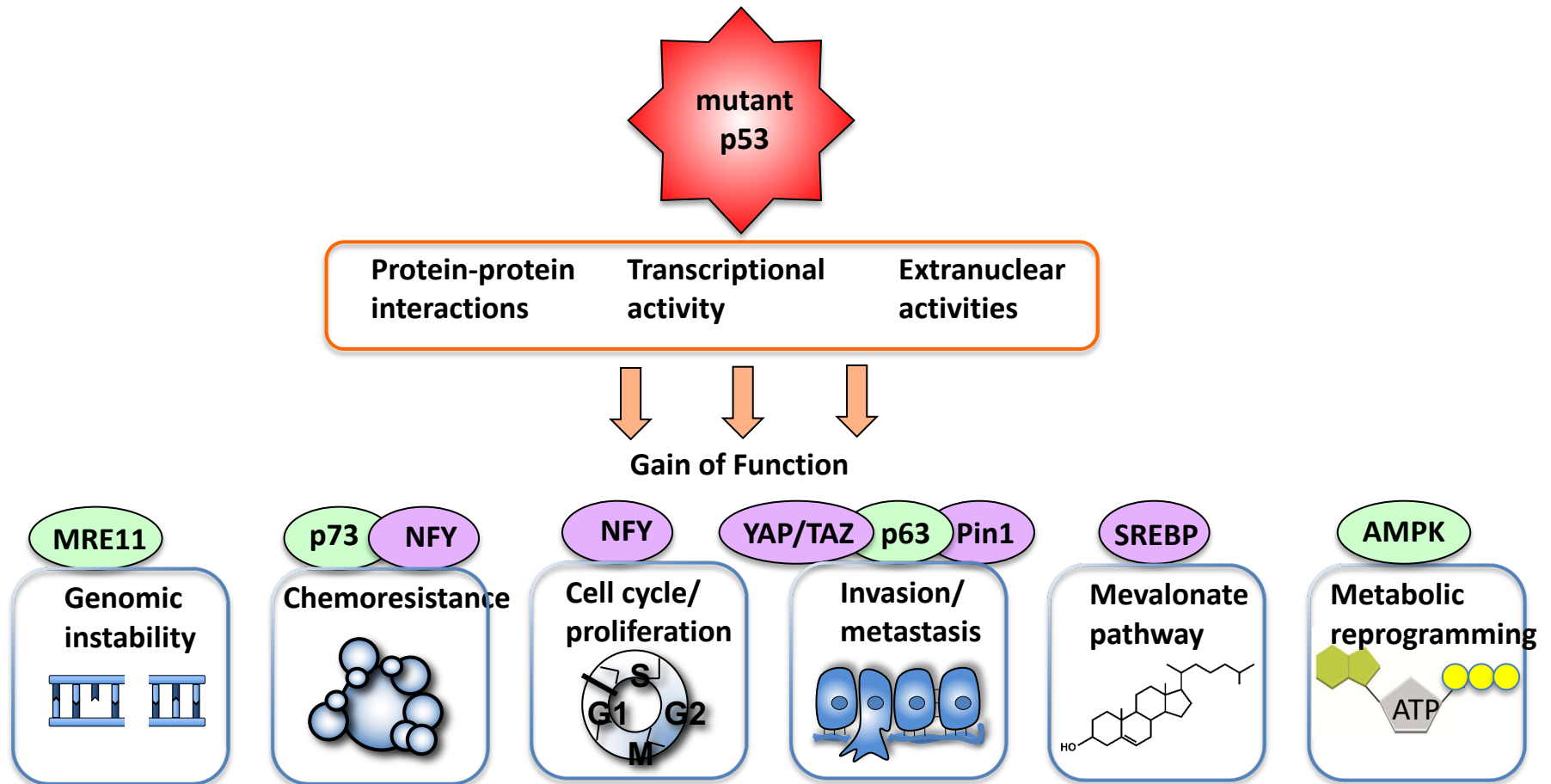


modified from Sabapathy and Lane, *Nat Rev Clin Oncol*, 2018

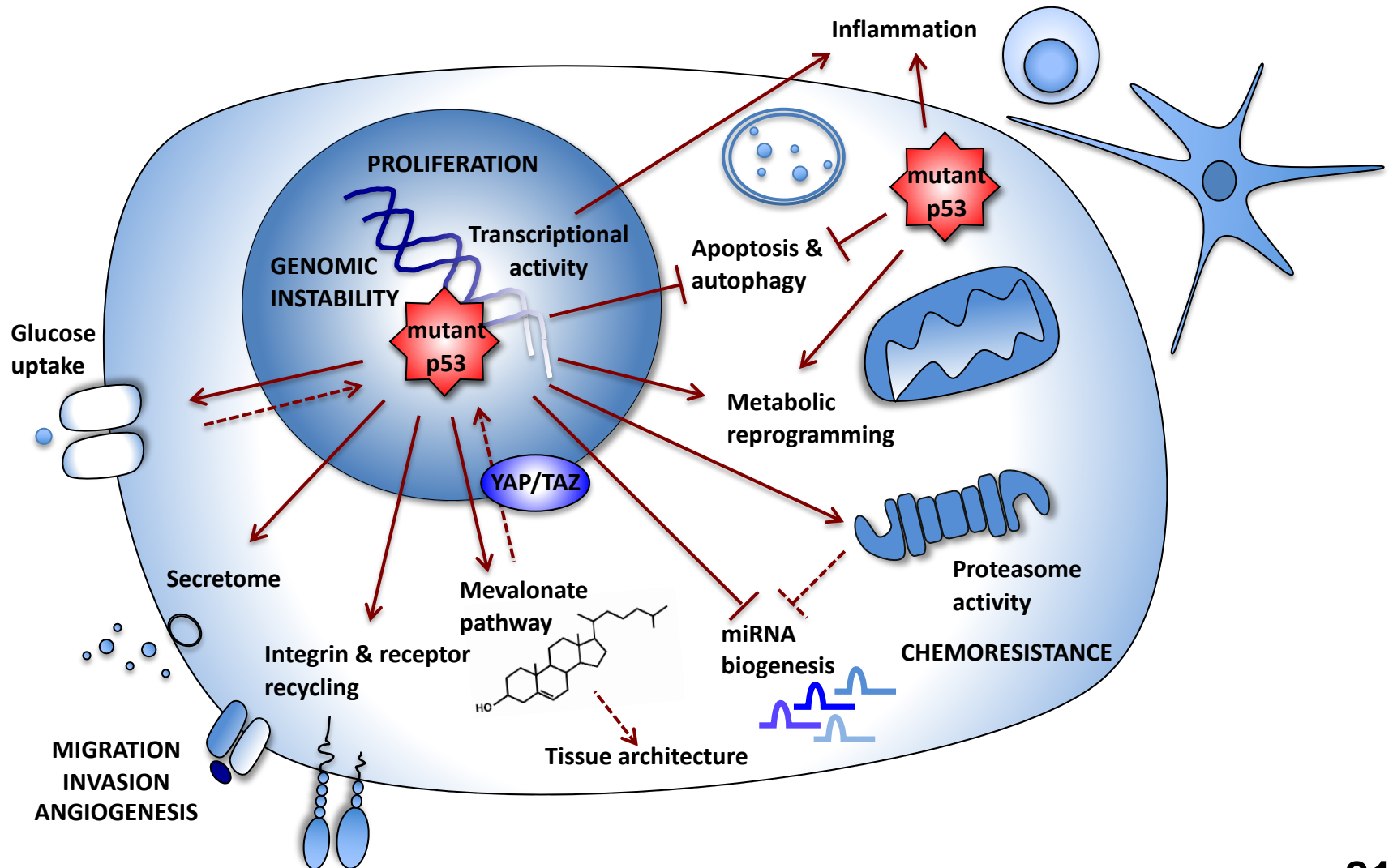
Functional consequences of *TP53* mutation



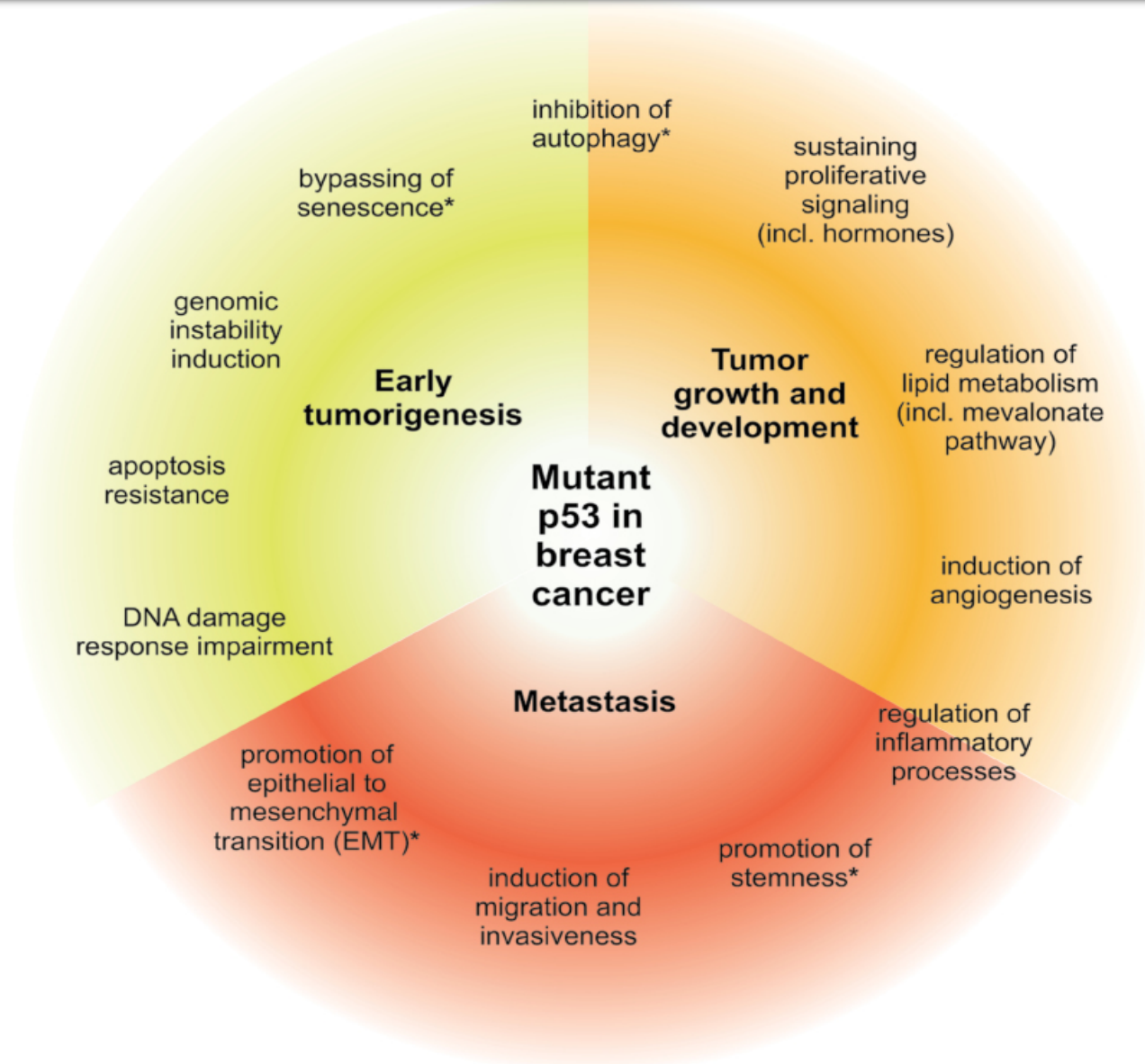
L'espressione di forme mutate di p53 conferisce vantaggi selettivi alle cellule tumorali



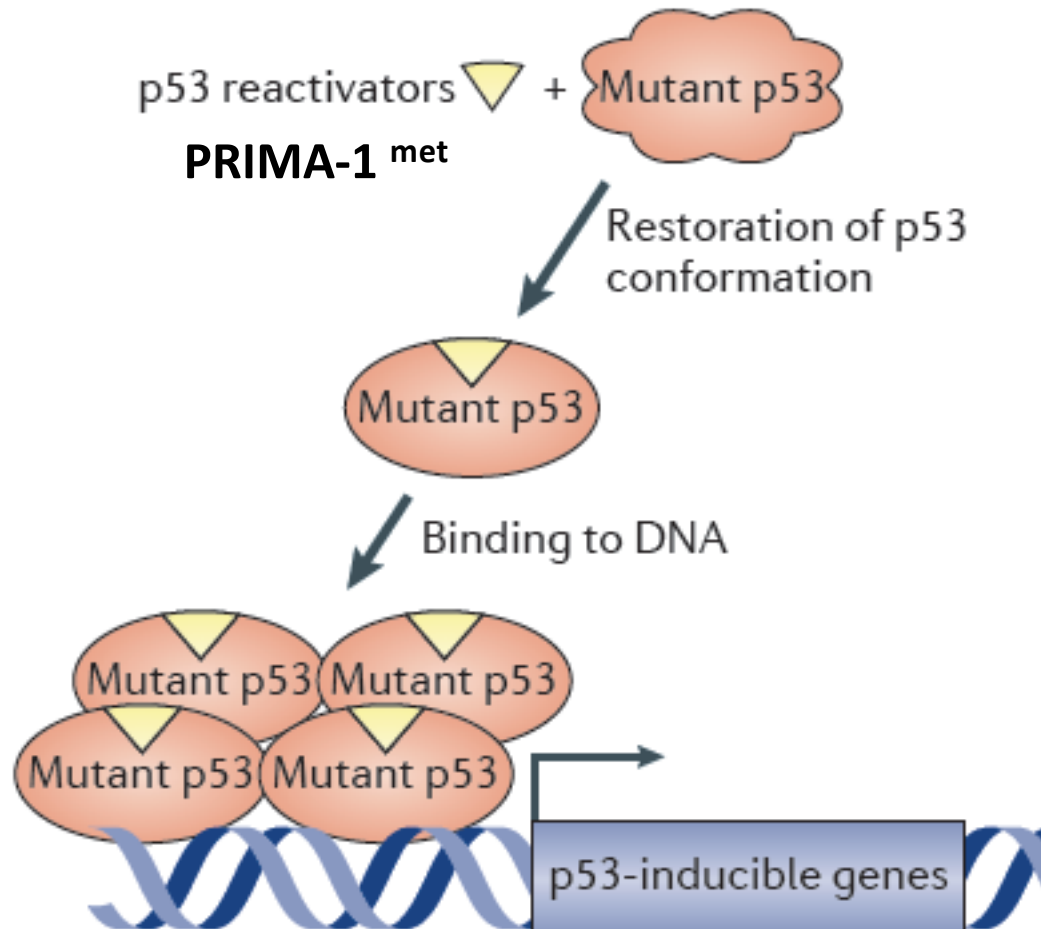
L'espressione di forme mutate di p53 conferisce vantaggi selettivi alle cellule tumorali



Mut-p53 promuove l'acquisizione dei cancer hallmarks

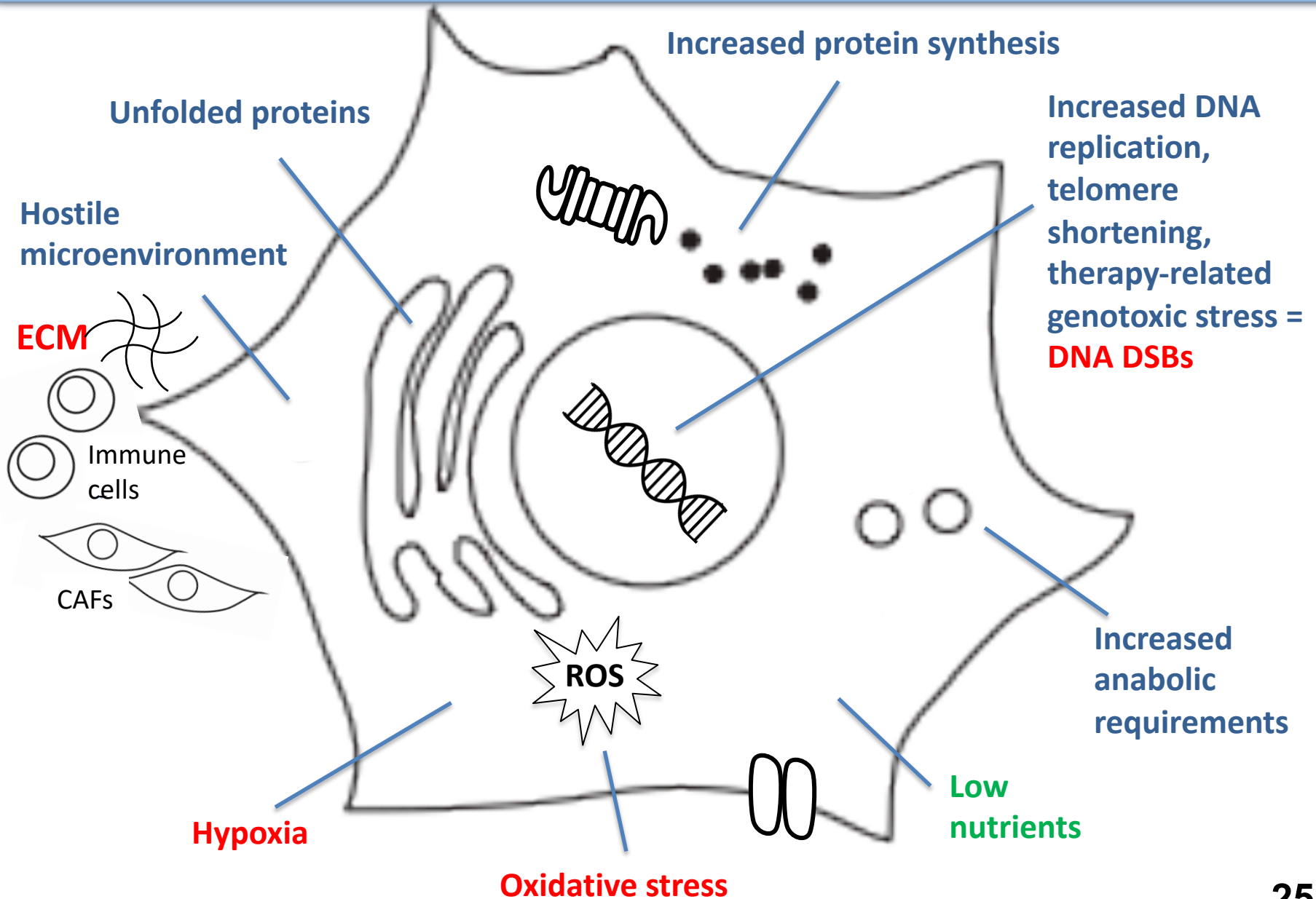


Approcci terapeutici: piccole molecole per ri-attivare la conformazione nativa di mut-p53



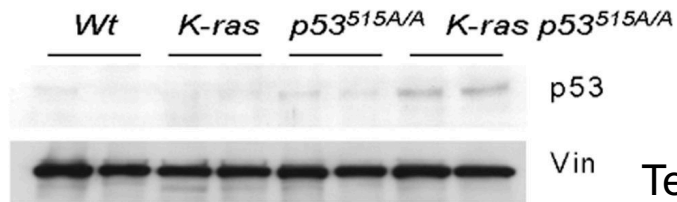
mutp53 è stabilizzata e attivata dalle condizioni di stress associate alla tumorigenesi

Le cellule tumorali sono sottoposte a molteplici stress



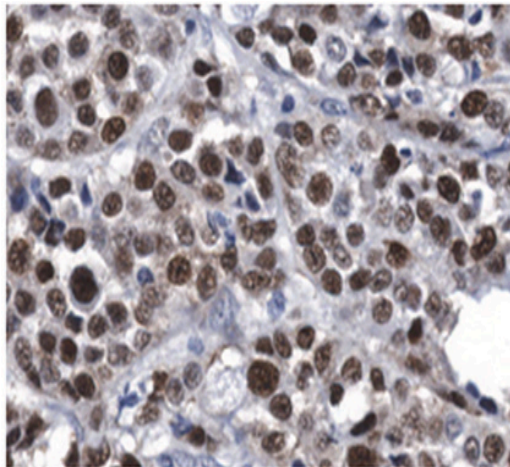
Mut-p53 è accumulata selettivamente nelle cellule tumorali

B

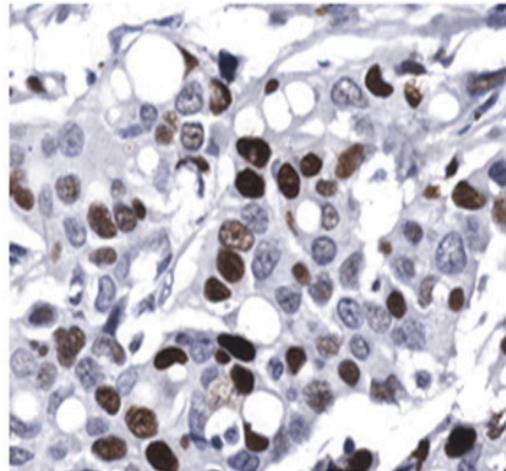


Terzian et al *Cancer Res* 2011

Mutp53 staining



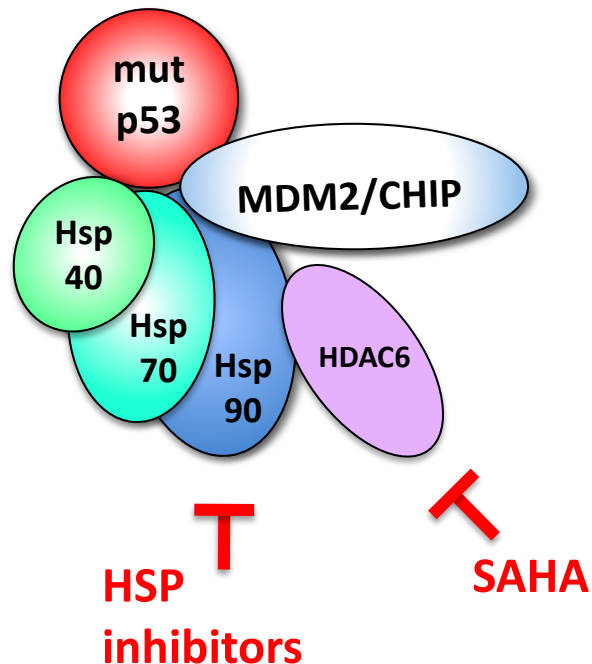
Breast cancers



endometrial

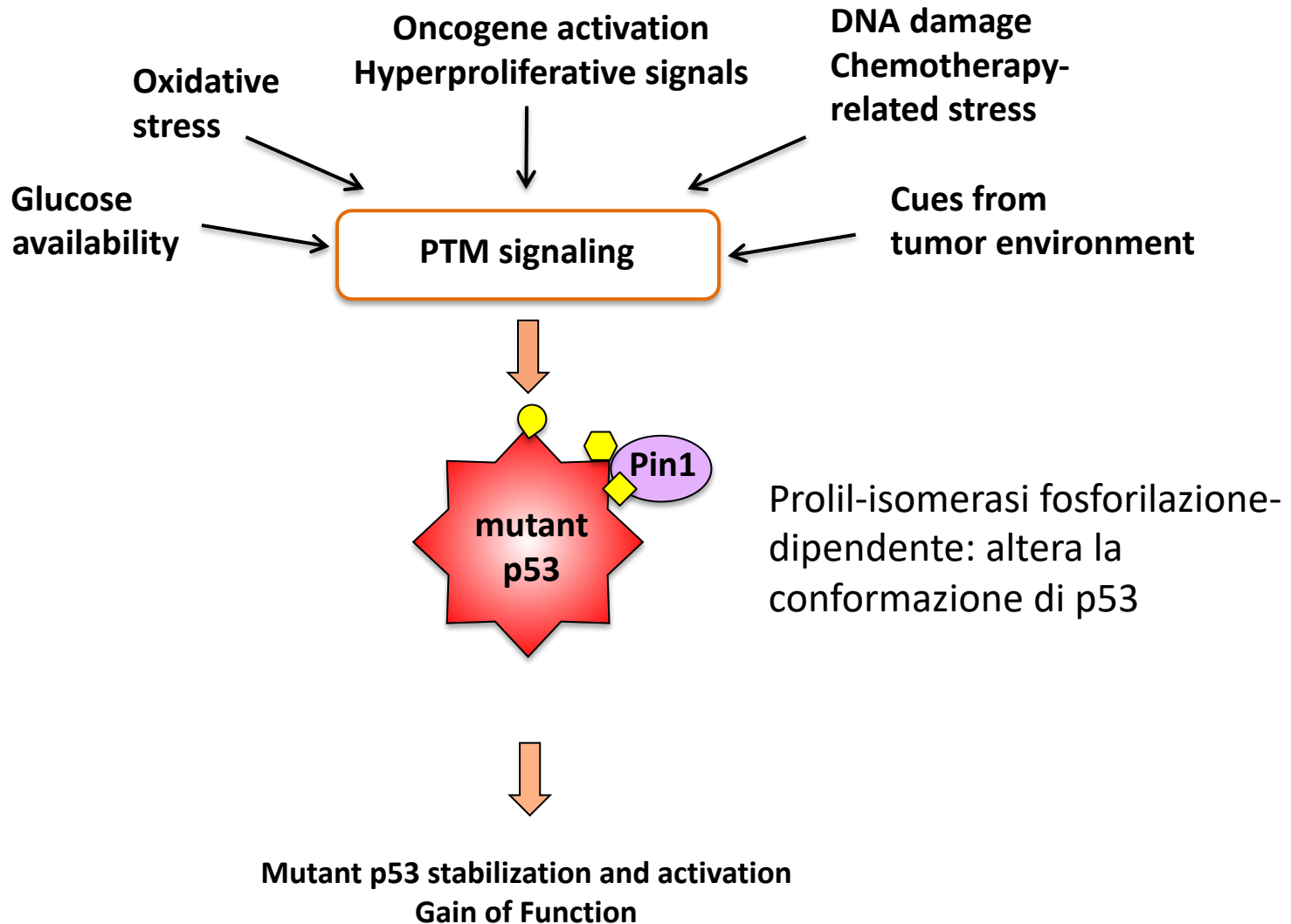
Bouchalova et al *J Pathol* 2014

Approccio terapeutico: riattivazione di ubiquitina ligasi che inducono degradazione di mutp53

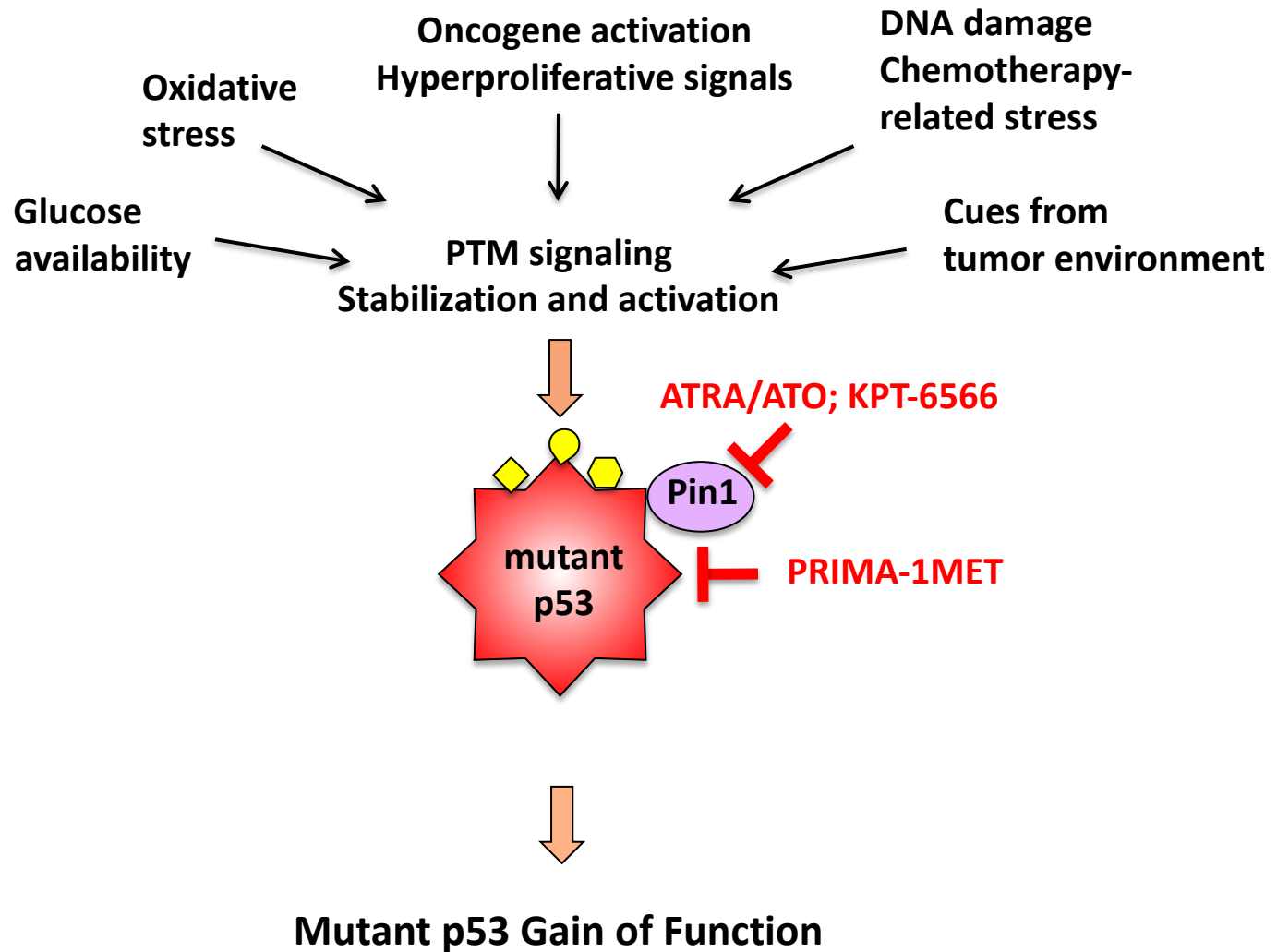


Pharmacological blockade elicits mutp53 destabilization and tumor regression in vivo

la segnalazione da stress porta a modificazioni di mut-p53



Implicazioni terapeutiche: inibizione di Pin1



Un gene, molte oncoproteine



Mutant p53: One, No One, and One Hundred Thousand

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