

Preclinical utility of GEM models of breast cancer



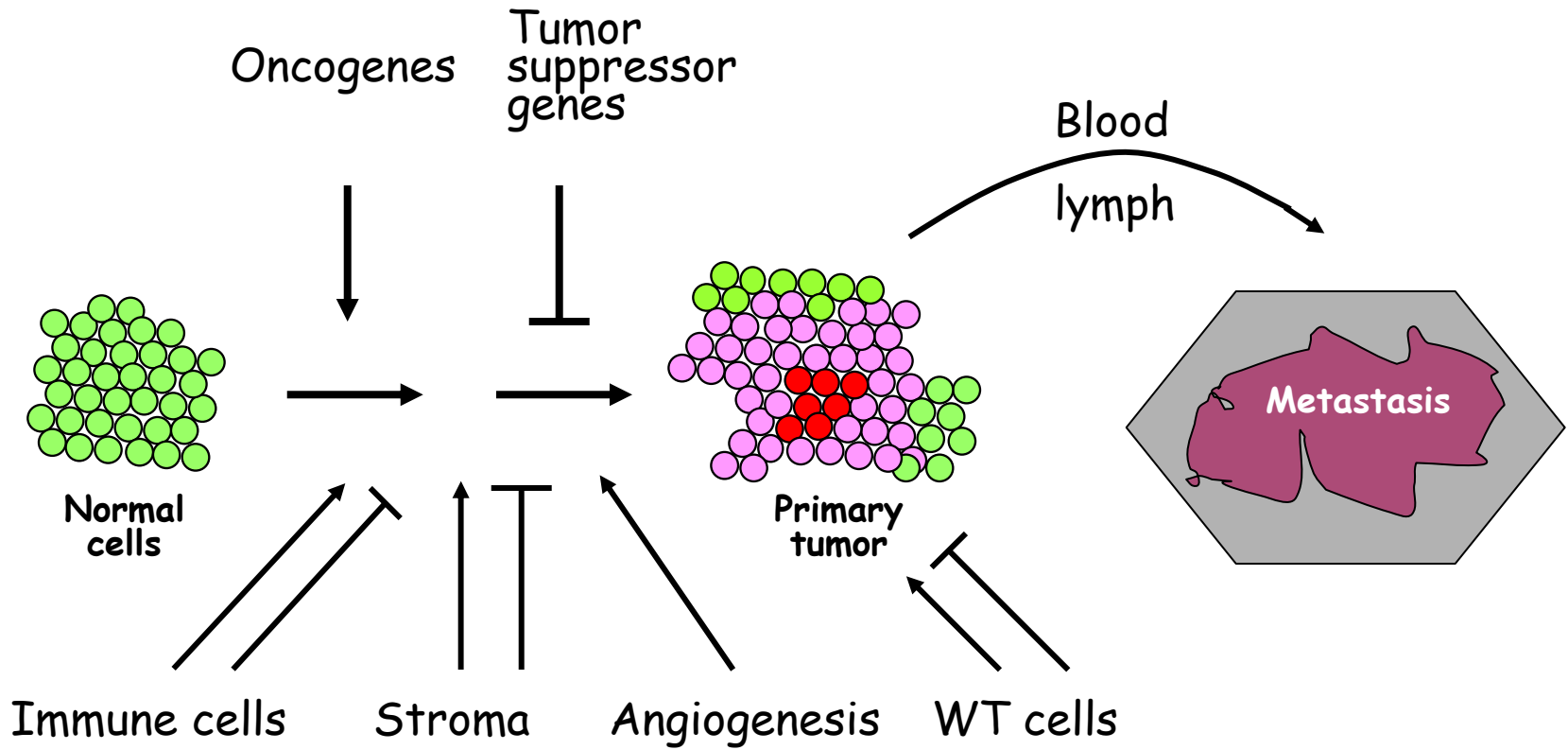
Royal Society workshop
London, 10 May 2010



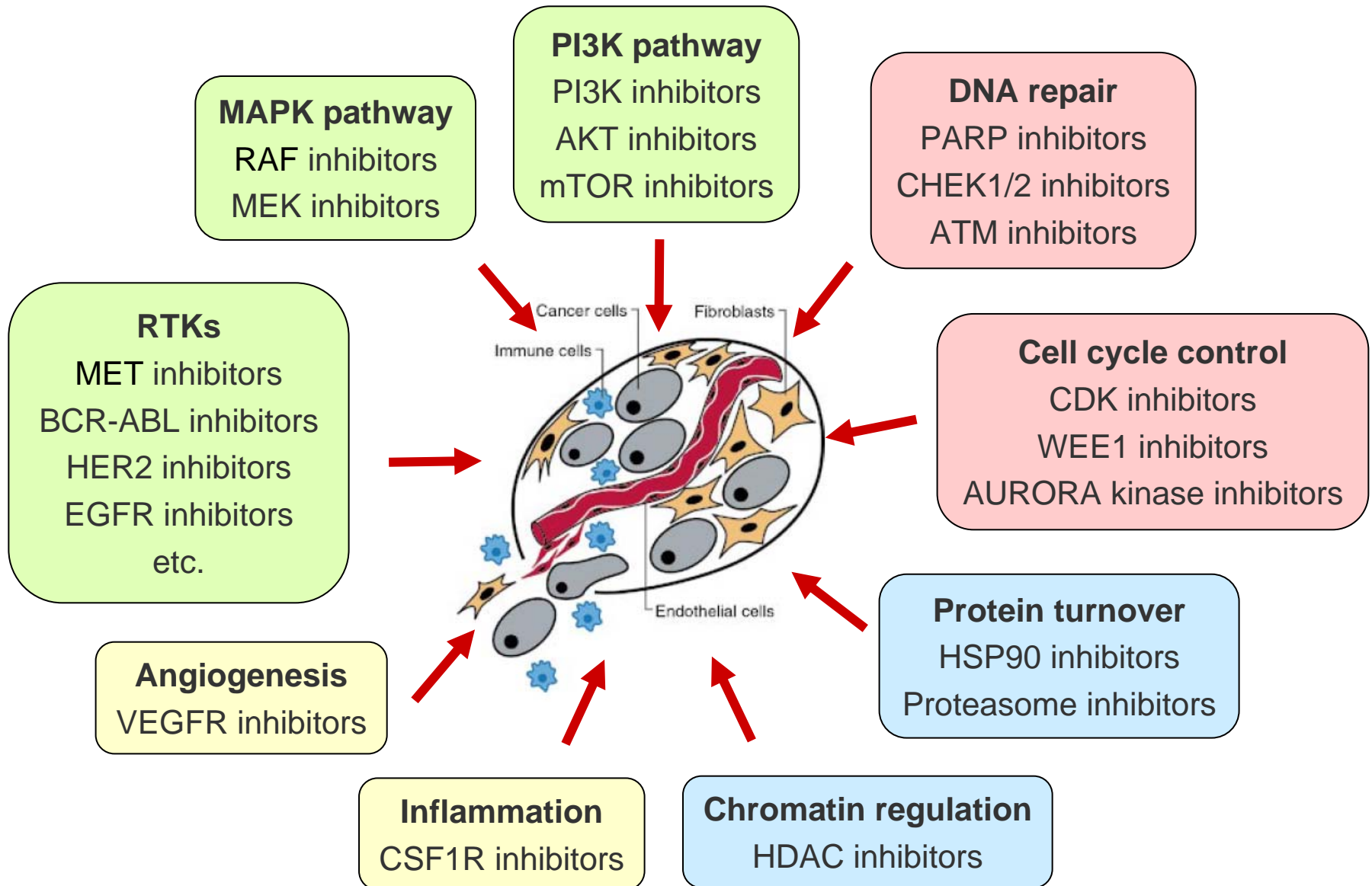
Jos Jonkers

Netherlands Cancer Institute, Amsterdam, The Netherlands

Factors controlling tumorigenesis



Targeting tumor cell signaling

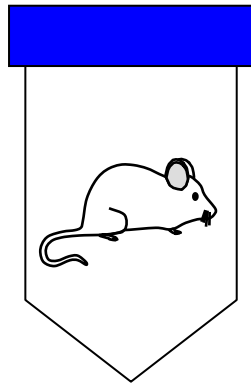


Classical xenograft models are poor predictors of clinical outcome



Xenograft models

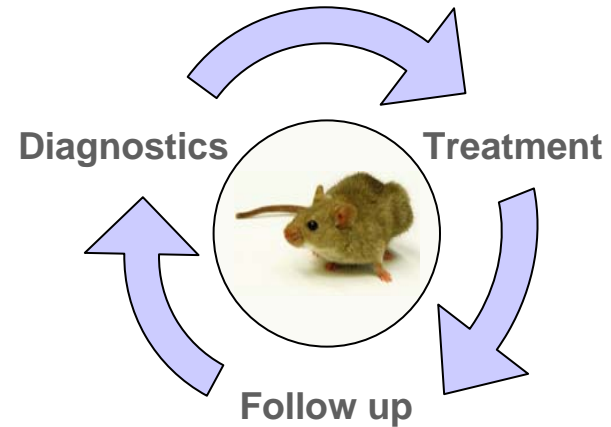
- Immunodeficient hosts
- Established tumor cell lines
- Do not mimic natural history of cancer development



- "In vivo test tubes"

Genetically engineered mice

- Immunoproticient host
- Real tumors
- Mimic sporadic development of de novo tumors in humans



- "Surrogate patients"

Genetically engineered mouse (GEM) models of human cancer

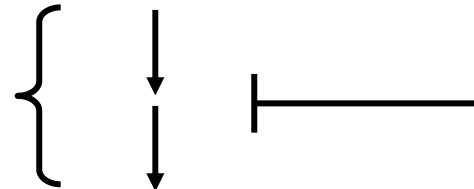


GEM model

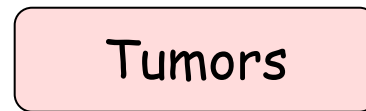


Early detection

Genotype-phenotype correlations
Tumor progression analysis
Cancer gene discovery



Prevention



Intervention
(compound testing,
target validation)



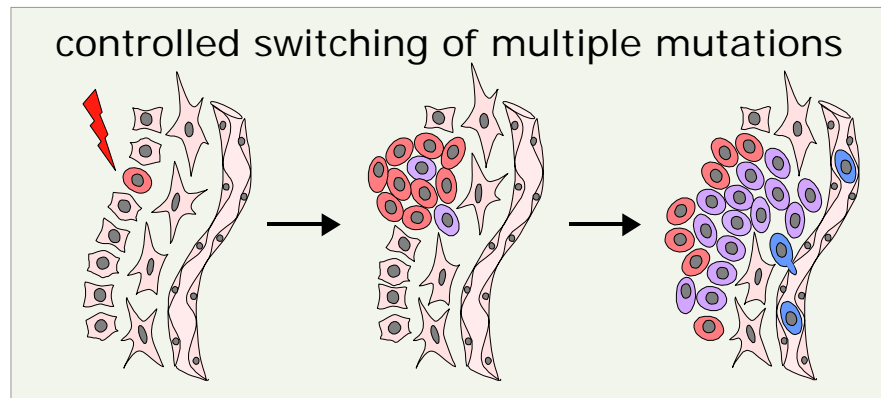
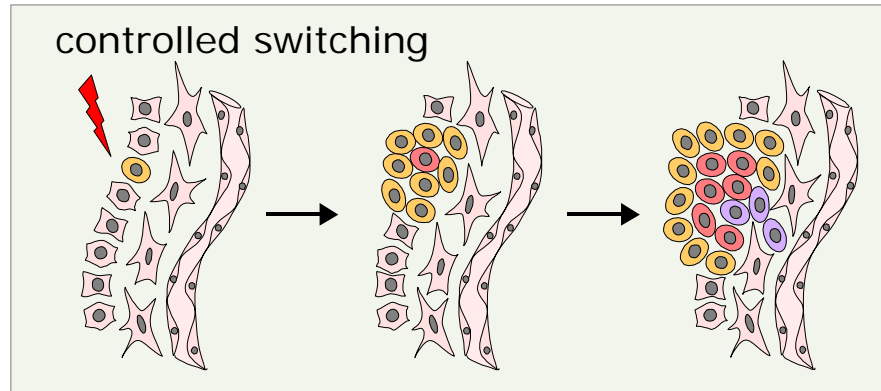
Intervention



Cross-resistance?
Mechanisms?

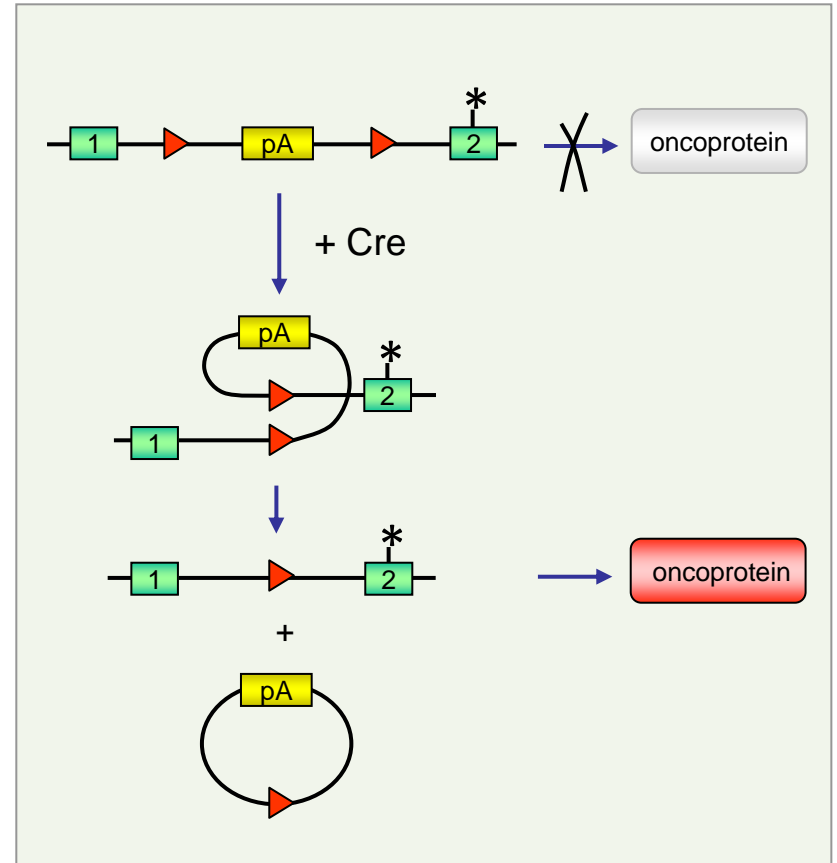
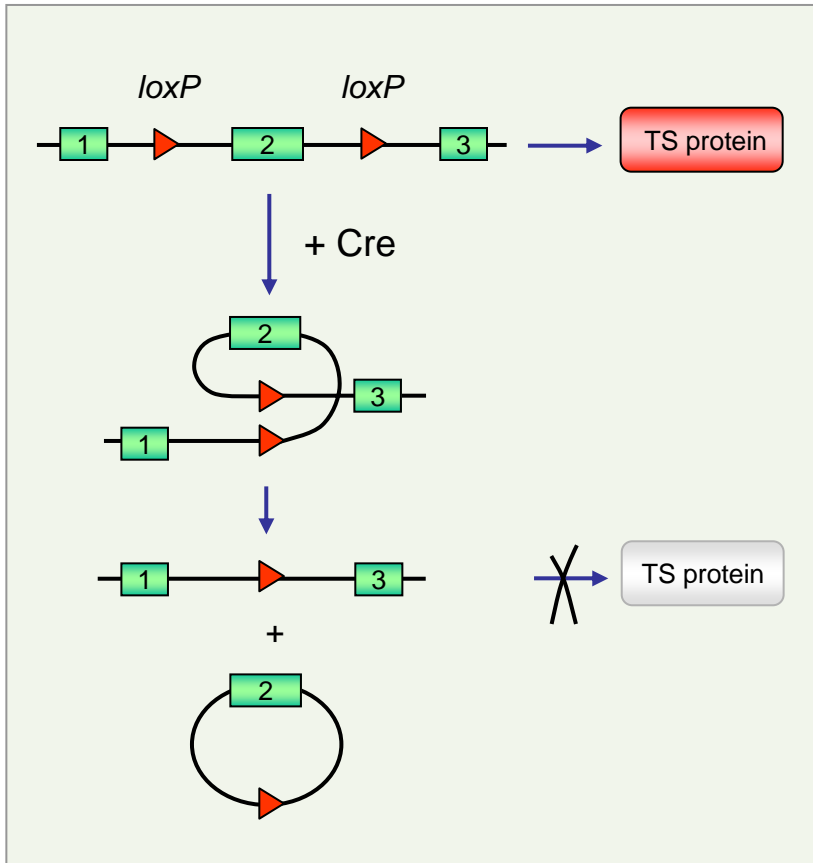


Reproducing sporadic human cancer in mice



- Epithelial cell with 1 mutation
- Epithelial cell with 2 mutations
- Epithelial cell with 3 or more mutations

Recombinase-mediated gene switching

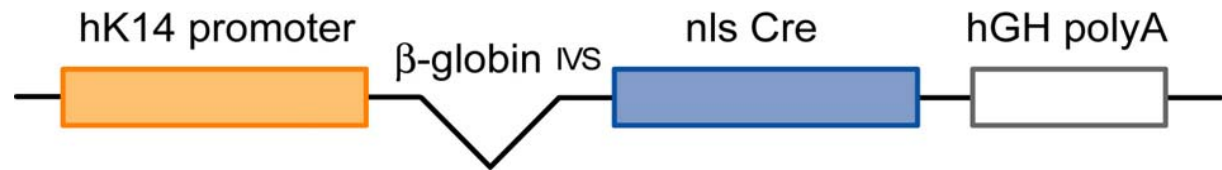


The BRCA1 mammary tumor model

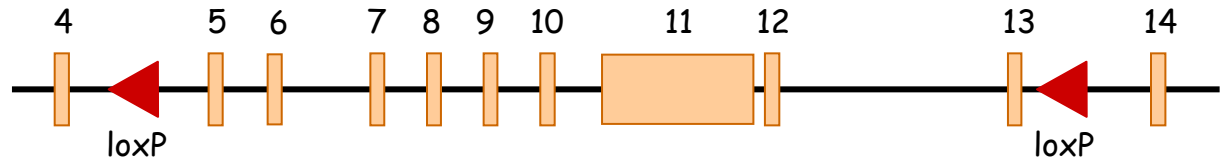


- Epithelium-specific inactivation of BRCA1 and p53

K14cre



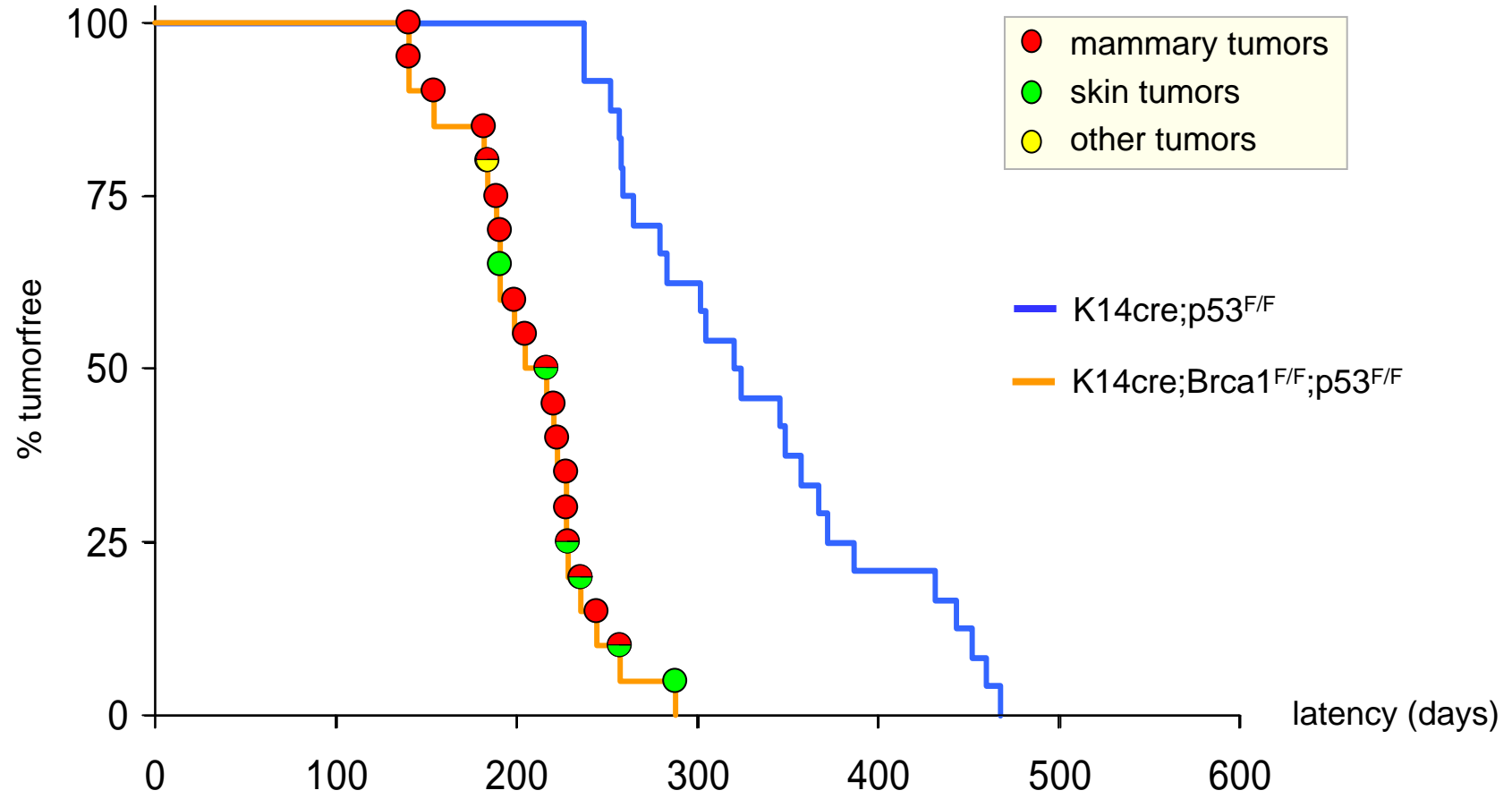
Brca1^F



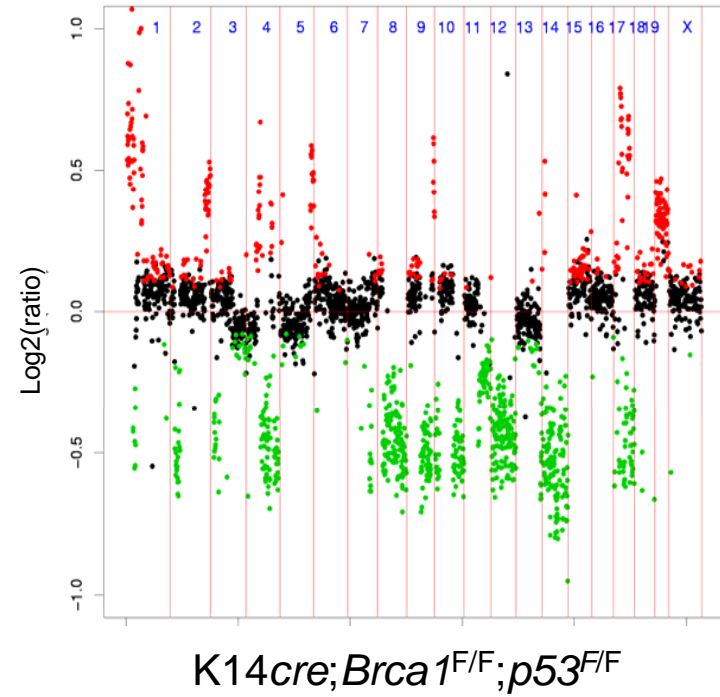
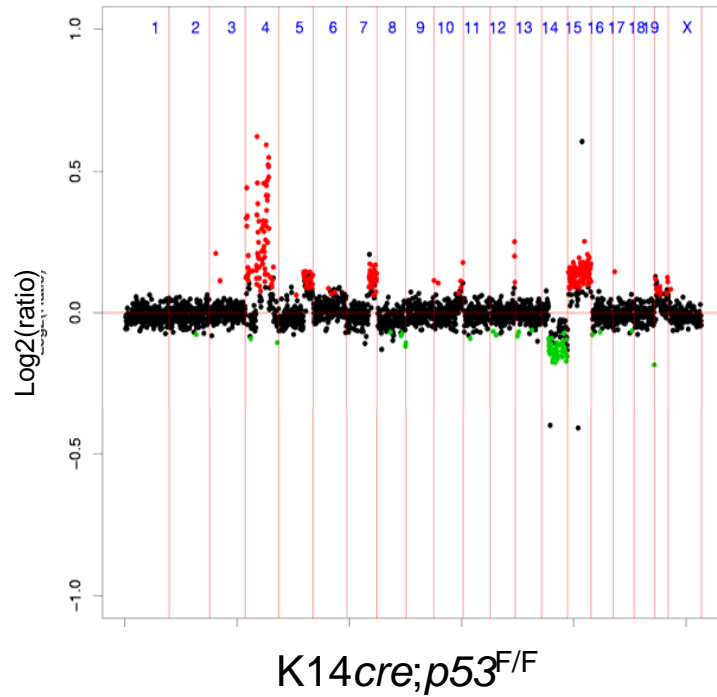
p53^F



Effects of BRCA1 and p53 loss on tumor formation



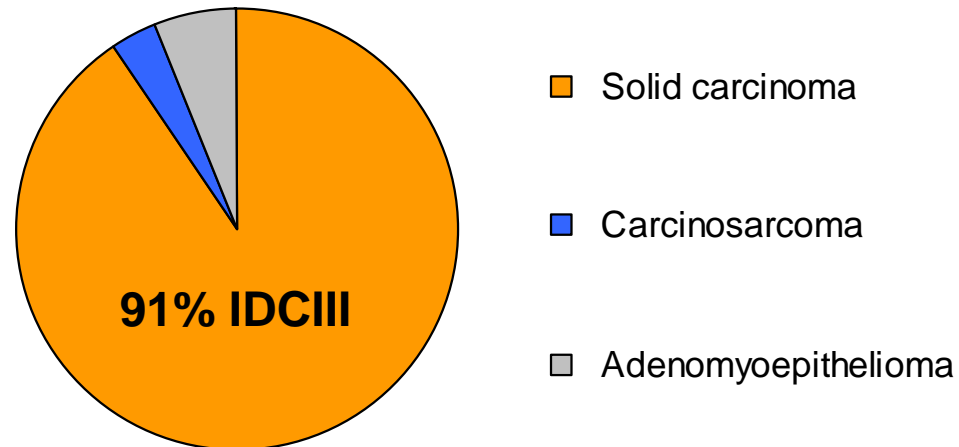
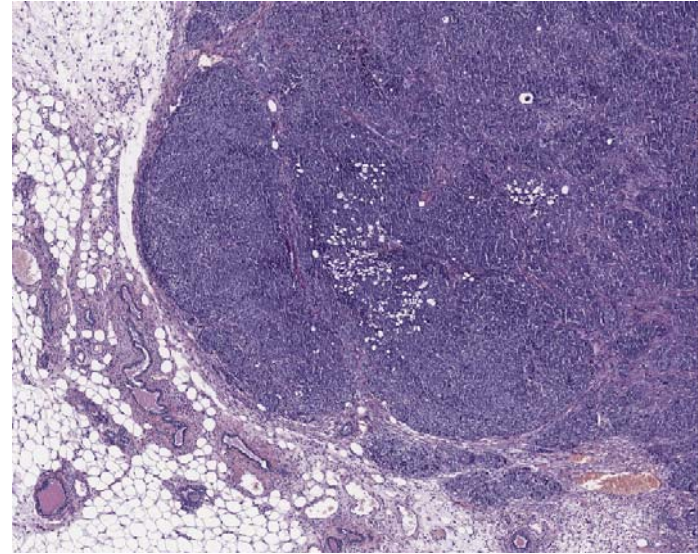
BRCA1 mouse mammary tumors display increased genomic instability



BRCA1 mouse mammary tumors resemble human BRCA1-associated breast cancer



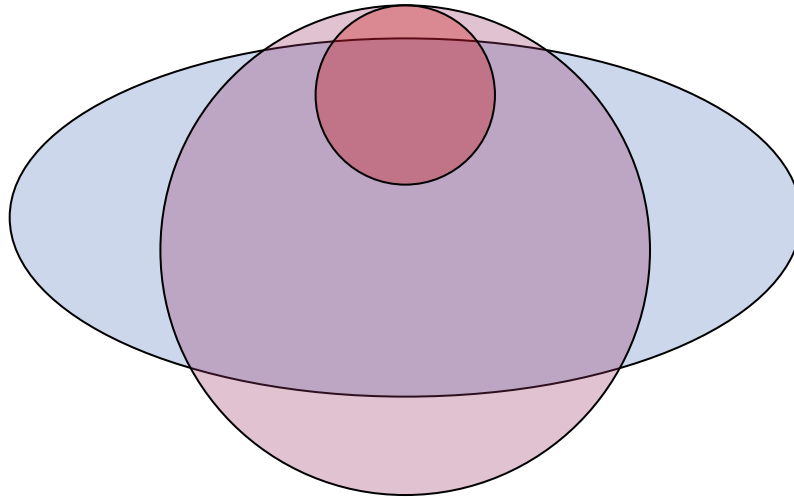
- Solid carcinoma (IDC nos)
- High-grade (III)
- Undifferentiated
- Pushing margins
- Triple-negative (ER⁻;PR⁻;HER2⁻)
- Basal-like (CK5⁺;CK14⁺)
- Genomic instability



BRCA1-mutated and BRCA1-like cancer



BRCA1-mutated (2-4%)

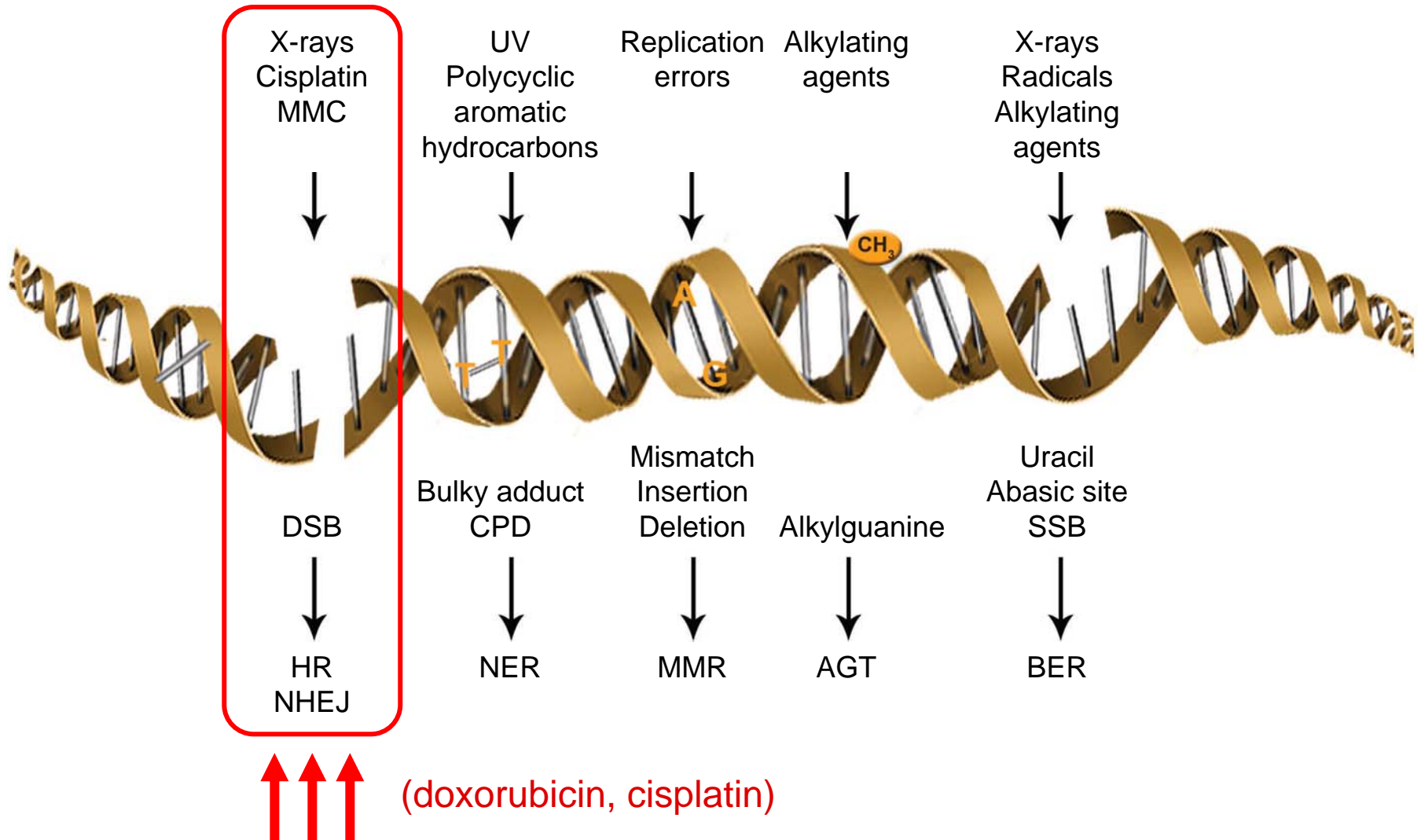


Triple-negative
(ER⁻ PR⁻ HER2⁻)
or basal-like (15%)
(39% in Afr-Am)

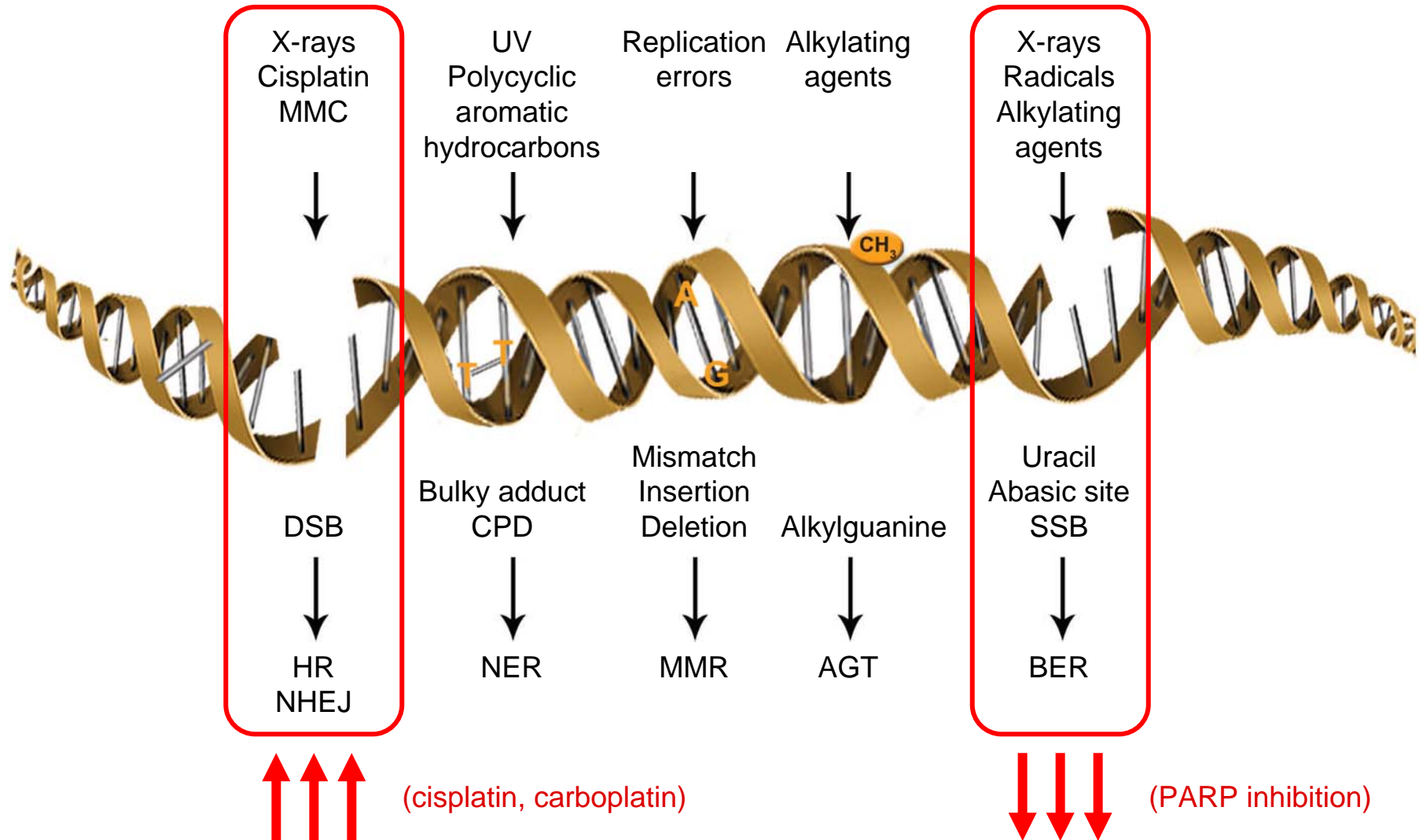
BRCA1-like (10-20%?)

- Triple-negative tumors have poor prognosis and rapid relapse
- Triple-negative breast tumors cannot be treated with endocrine agents or HER2 targeted therapy

Targeting HR deficiency in the BRCA1 mammary tumor model



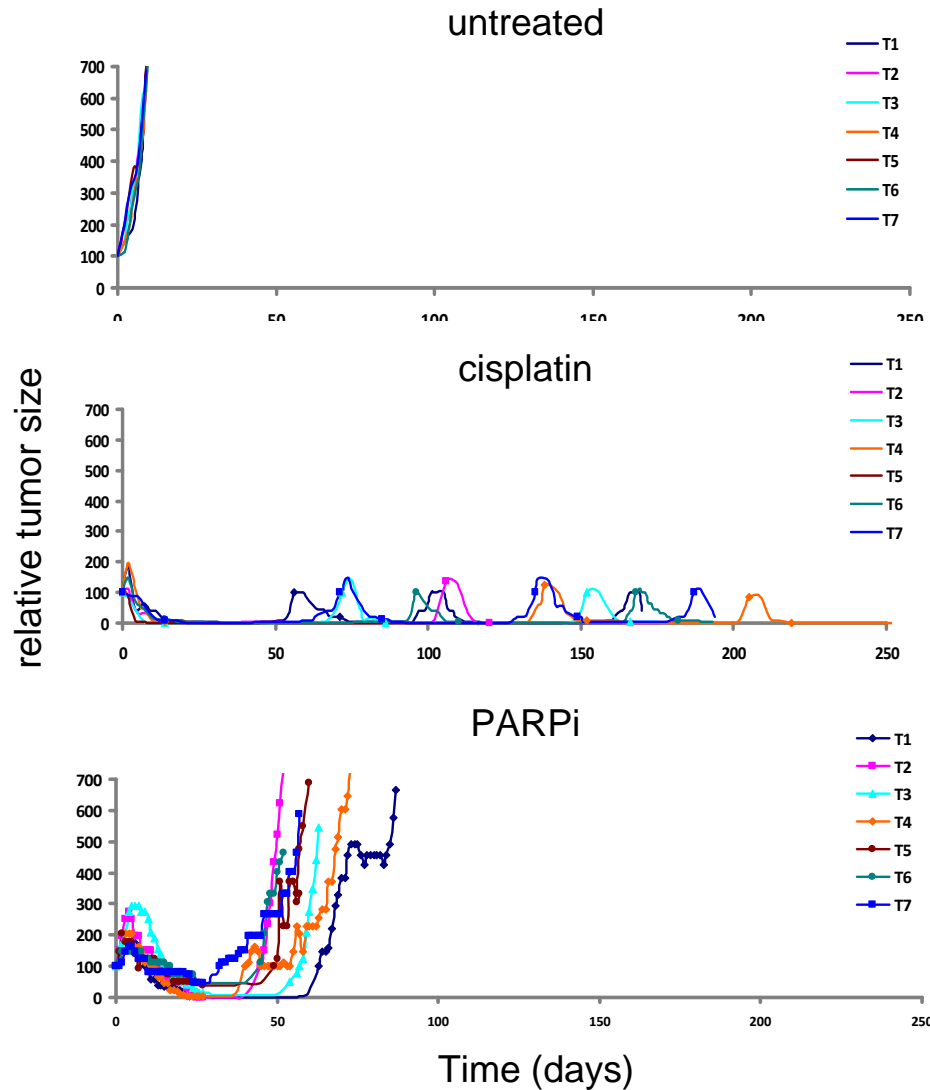
Targeting HR deficiency in the BRCA1 mammary tumor model



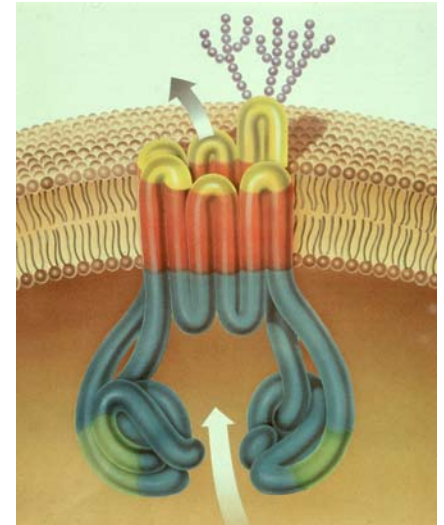
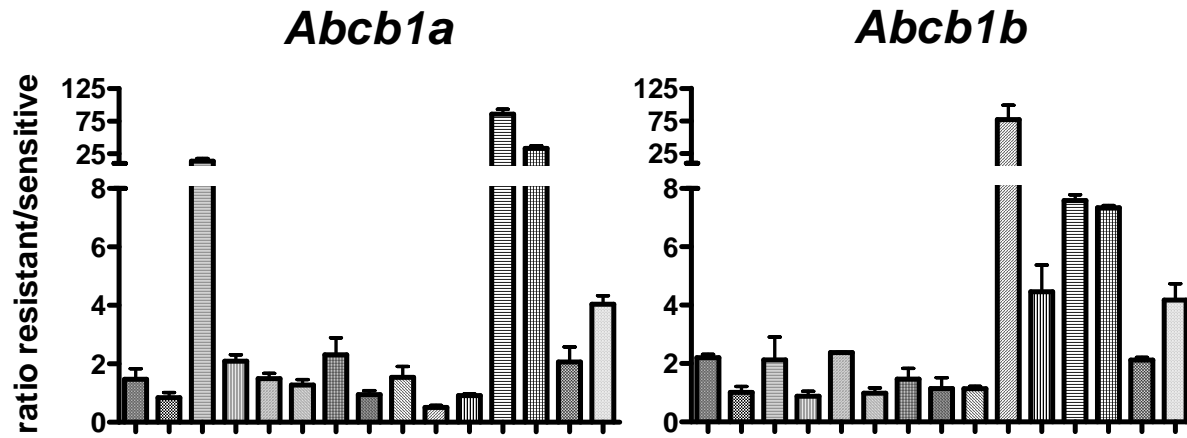
Therapy response and resistance in the BRCA1 mammary tumor model



Brca1^{-/-};*p53*^{-/-}



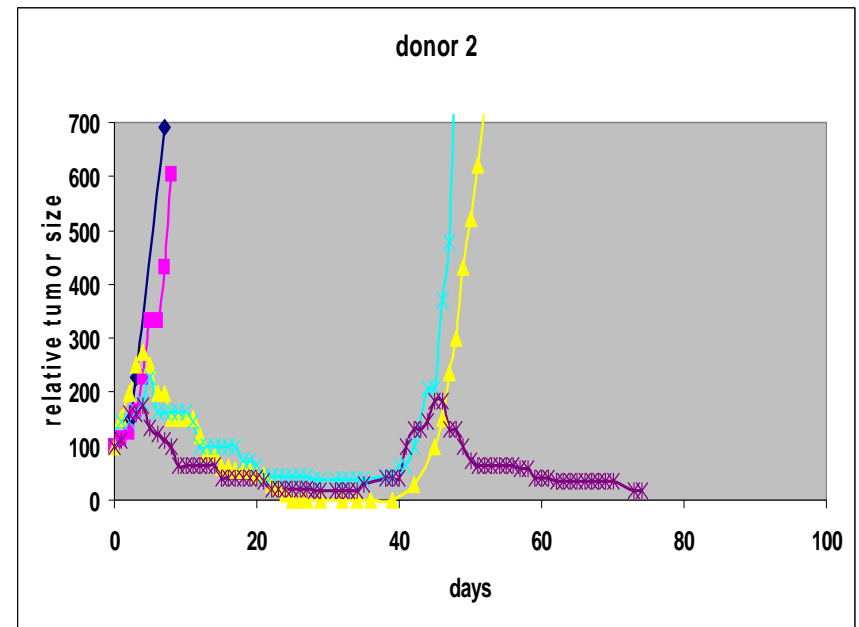
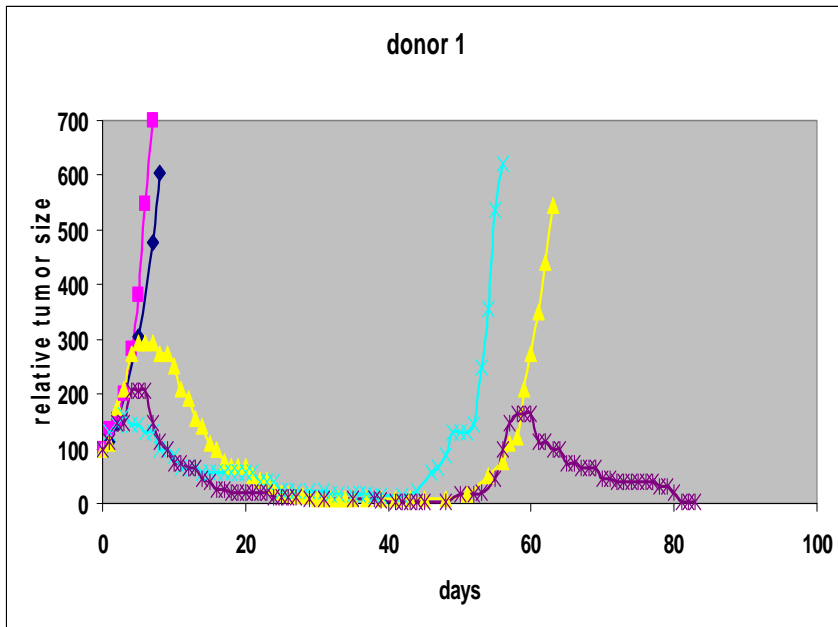
Increased expression of *Abcb1a* and *Abcb1b* in PARPi-resistant tumors



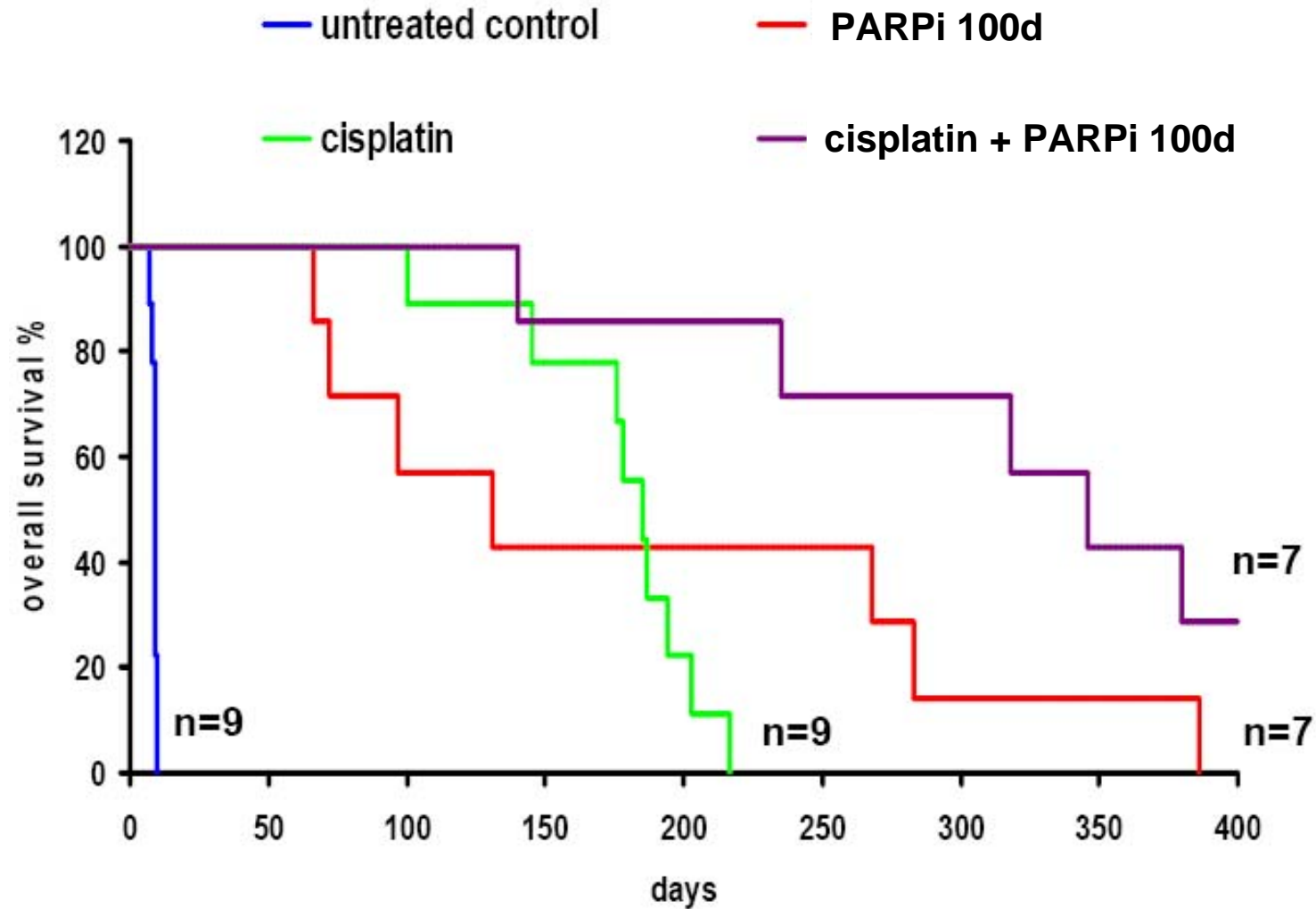
Reversal of oalaprib resistance by P-gp inhibition



- ◆ untreated control
- vehicle
- ▲ PARPi 28d relapse PARPi
- ✕ PARPi 28d, relapse P-gpi
- ✱ PARPi 28d, relapse PARPi + P-gpi

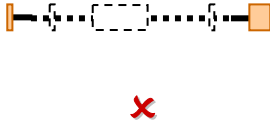
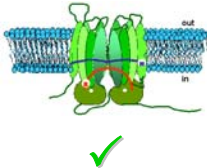



Treatment of BRCA1-deficient mammary tumors with cisplatin and olaparib



BRCA1 mammary tumor models for therapy response and resistance



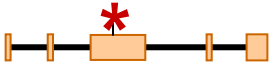
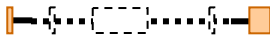
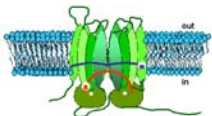
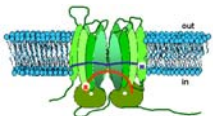
		K14cre; Brca1^{F/F}; p53^{F/F}	
Genetic reversion			
Pgp activation			
Other			

BRCA1 mammary tumor models for therapy response and resistance



Brca1^{185delAG}
Brca1^{C61G}
Brca1^{5382insC}



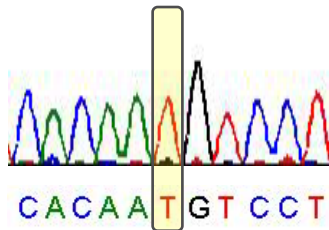
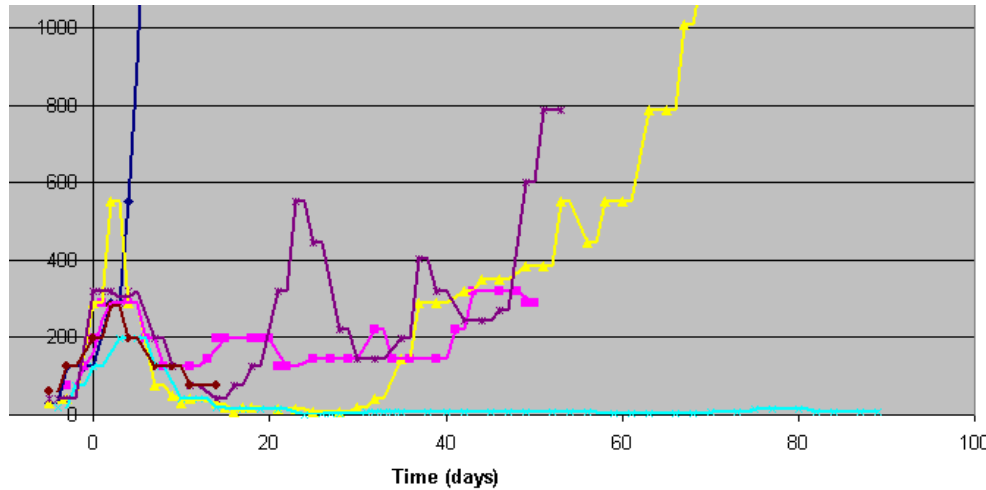
	K14cre; Brca1 ^{Tr/F} ; p53 ^{F/F}	K14cre; Brca1 ^{F/F} ; p53 ^{F/F}	
Genetic reversion	 ✓	 ✗	
Pgp activation	 ✓	 ✓	
Other	✓	✓	

BRCA1-C61G mammary tumors acquire resistance to cisplatin

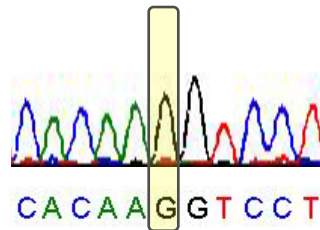


No Ub ligase activity

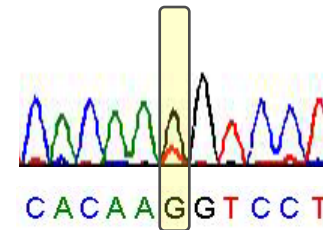
No interaction with BARD1



Wild type *Brca1*

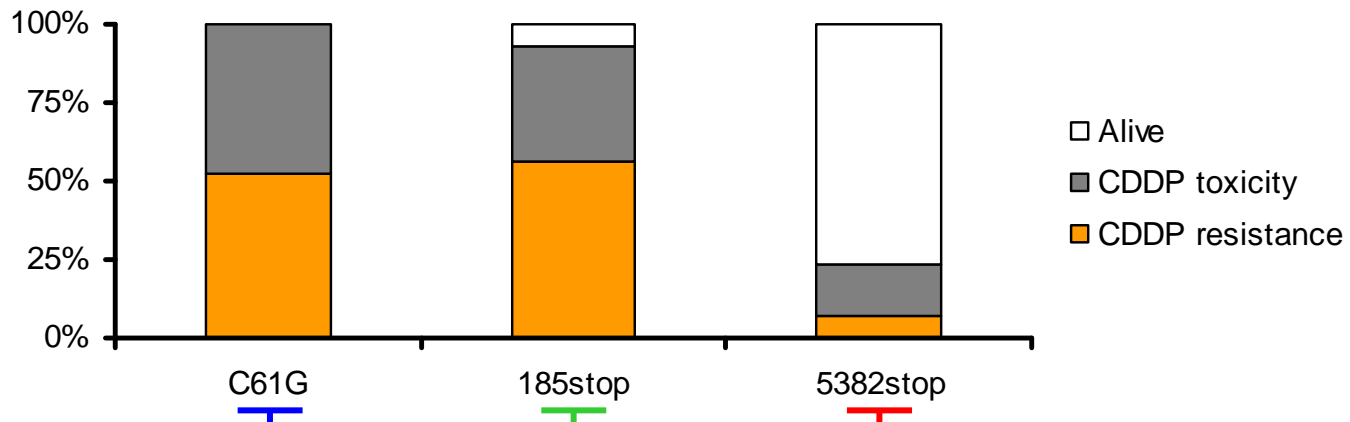
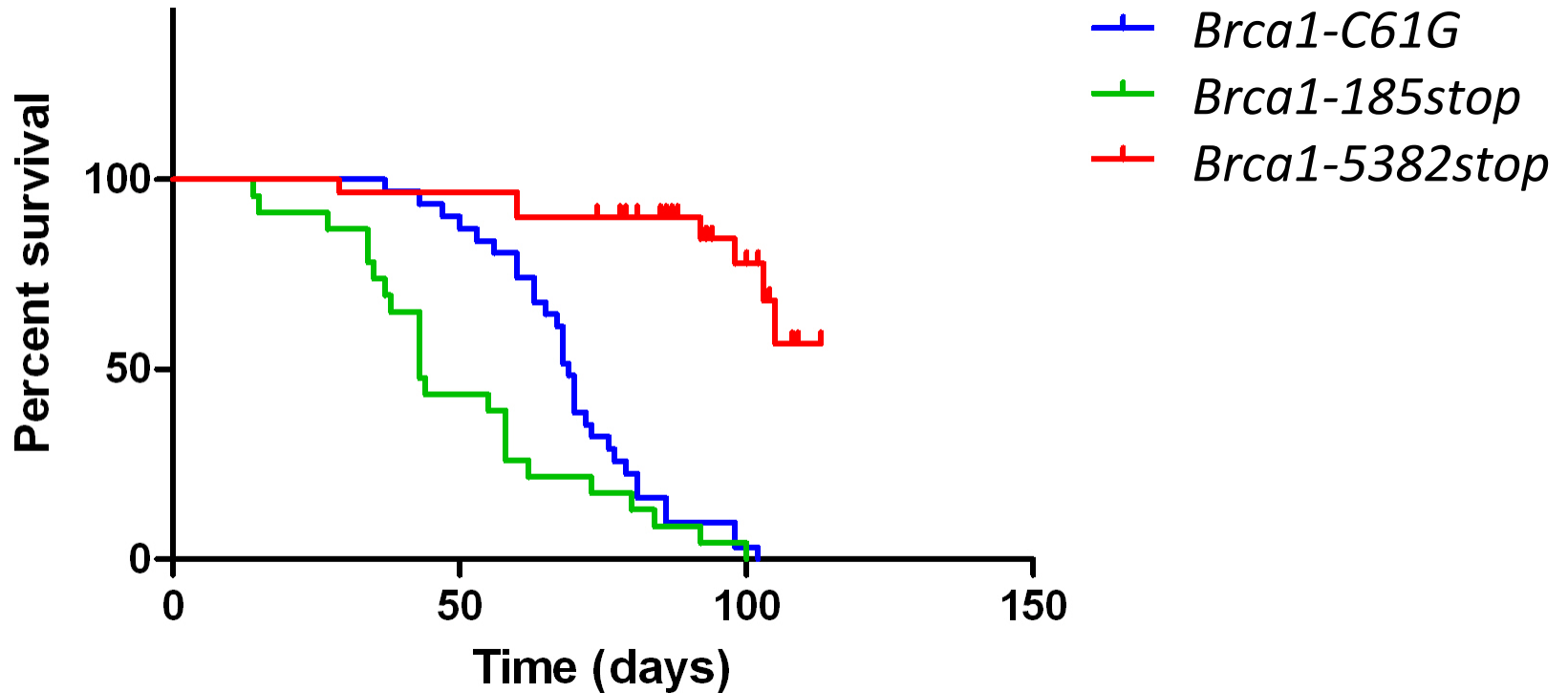


Cisplatin-sensitive
Brca1^{C61G} tumor



cisplatin-resistant
Brca1^{C61G} tumor

Overall survival following cisplatin therapy

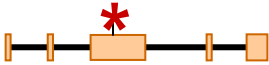
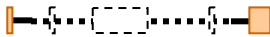

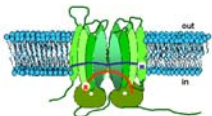
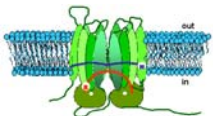
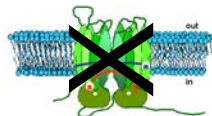


BRCA1 mammary tumor models for therapy response and resistance



Brca1^{185delAG}
Brca1^{C61G}
Brca1^{5382insC}

Mrd1^{-/-}

	K14cre; Brca1 ^{Tr/F} ; p53 ^{F/F}	K14cre; Brca1 ^{F/F} ; p53 ^{F/F}	K14cre; Brca1 ^{F/F} ; p53 ^{F/F} ; Mdr1 ^{-/-}
Genetic reversion	 ✓	 ✗	 ✗
Pgp activation	 ✓	 ✓	 ✗
Other	✓	✓	✓

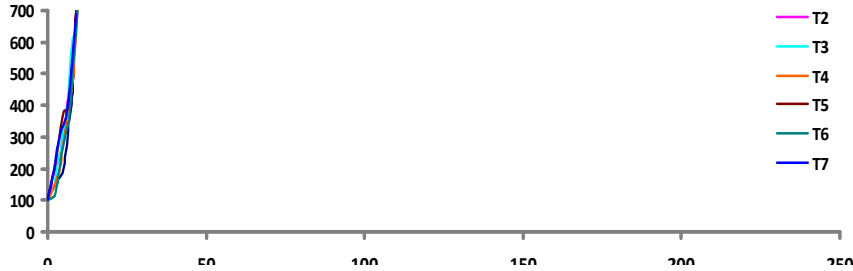
Acquired resistance to olaparib in the Pgp-deficient BRCA1 mammary tumor model



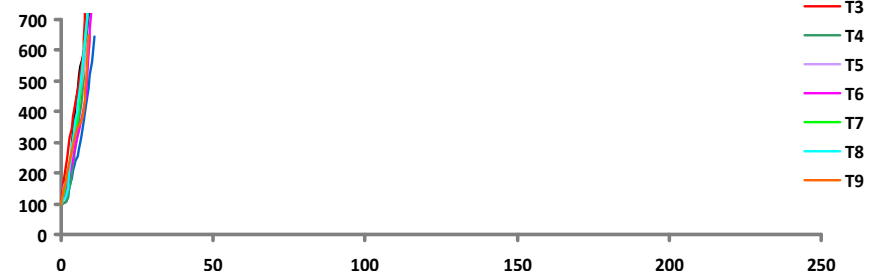
Brca1^{-/-};*p53*^{-/-}

Brca1^{-/-};*p53*^{-/-};*Mdr1*^{-/-}

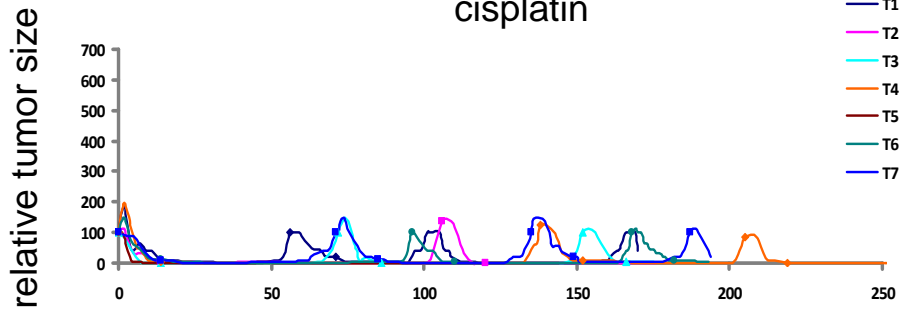
untreated



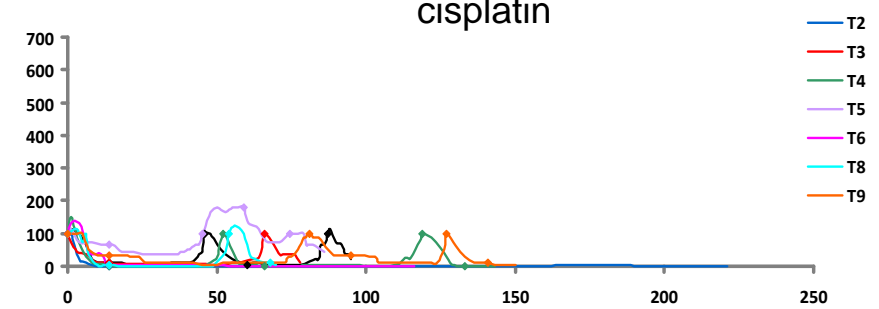
untreated



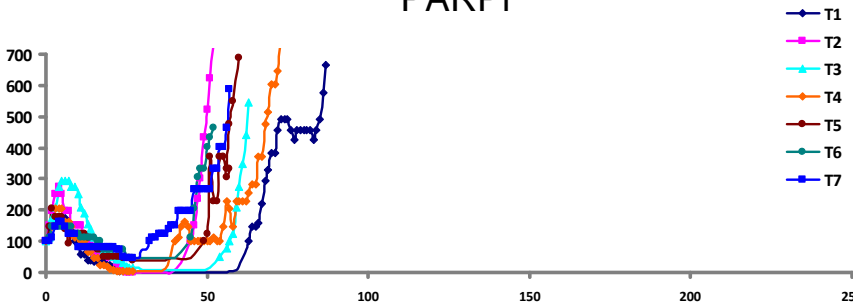
cisplatin



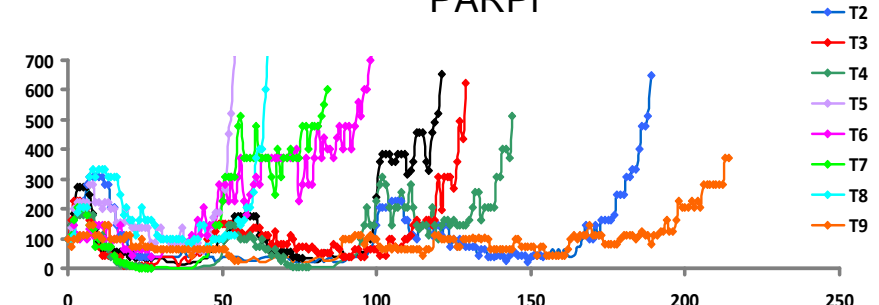
cisplatin



PARPi



PARPi

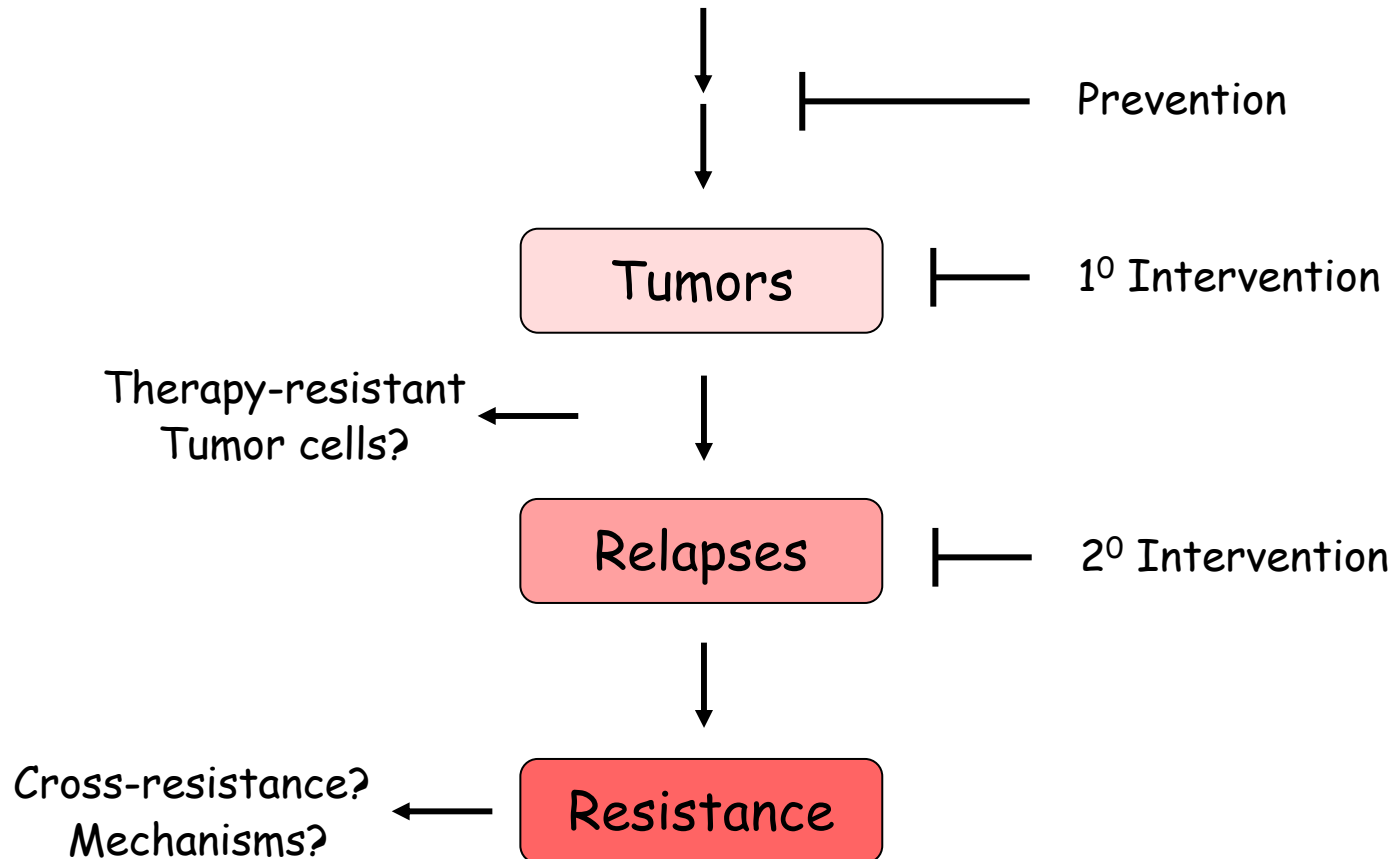


Time (days)

GEM models of human cancer



GEM model



Acknowledgements



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- ✓ Marina Pajic

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