

Dissection of breast cancer development and therapy resistance in mouse models



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GEMMs of human cancer

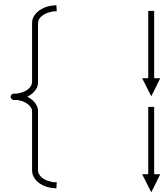


Genetically engineered
mouse models (GEMMs)



Early detection

Cancer gene discovery
Cancer gene validation



Prevention

Tumors

Drug target validation
Therapeutic intervention

Minimal residual disease

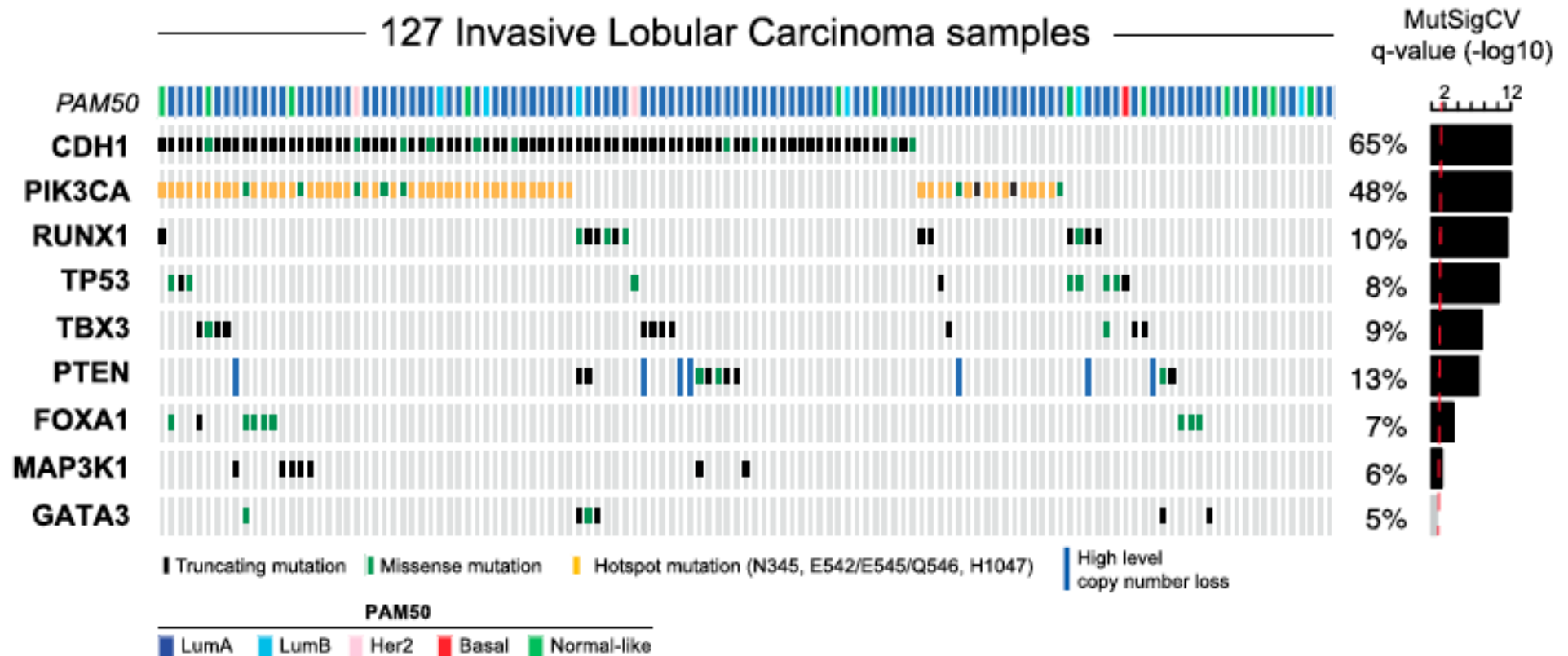
Relapses

Therapeutic intervention

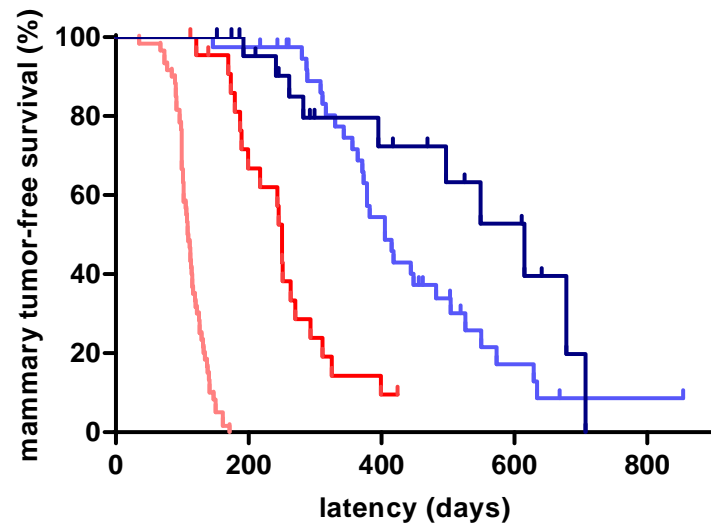
Resistance mechanisms

Resistance

Invasive Lobular Breast Carcinoma (ILC)

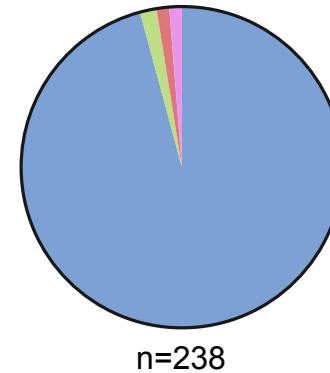


E-cadherin and Pten loss induces classic ILC

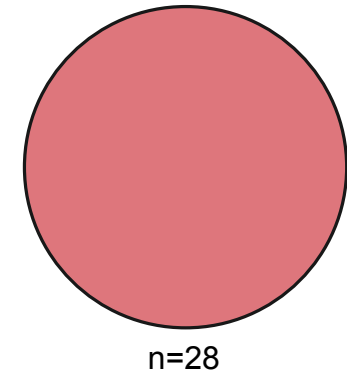


— WAPcre;*Pten*^{+/F} (n=26) | ns
 — WAPcre;*Cdh1*^{F/F};*Pten*^{+/F} (n=39) | ns
 — WAPcre;*Pten*^{F/F} (n=23) | p < 0.0001
 — WAPcre;*Cdh1*^{F/F};*Pten*^{F/F} (n=60) | p < 0.0001

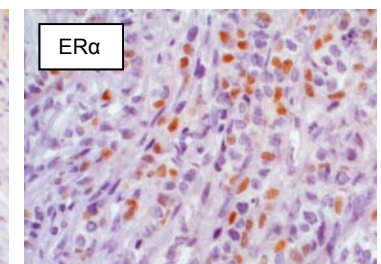
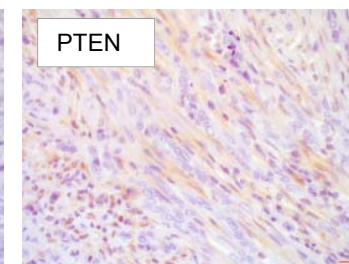
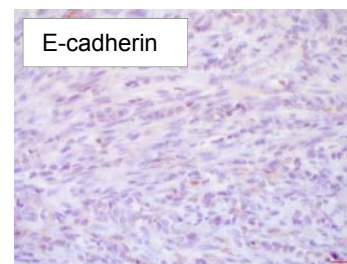
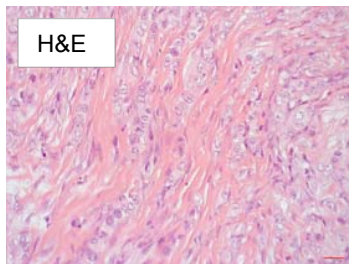
WAPcre;*Cdh1*^{F/F};*Pten*^{F/F}



WAPcre;*Pten*^{F/F}



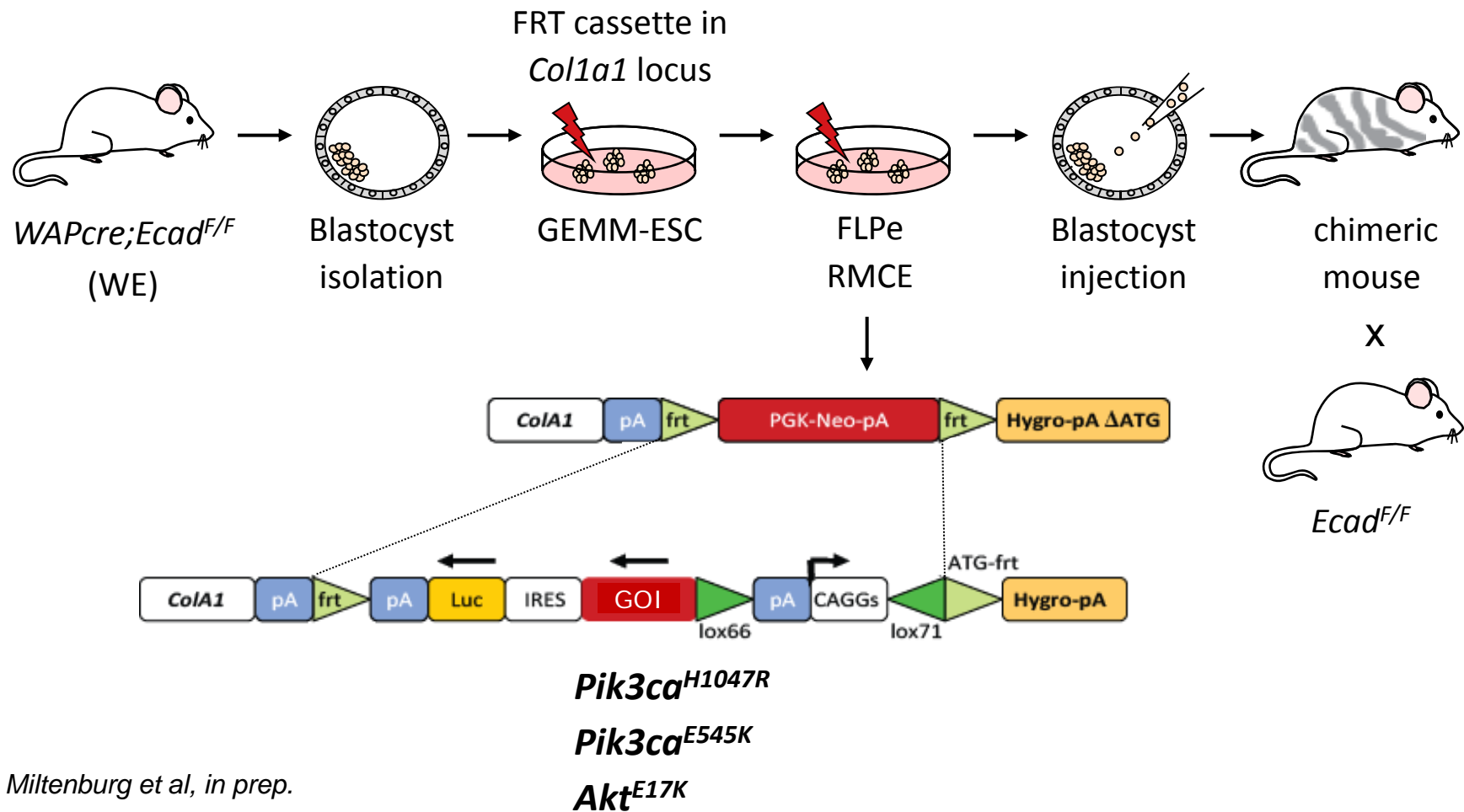
■ ILC, classical subtype
 ■ ILC, solid subtype
 ■ solid carcinoma
 ■ squamous metaplastic carcinoma
 ■ EMT tumor



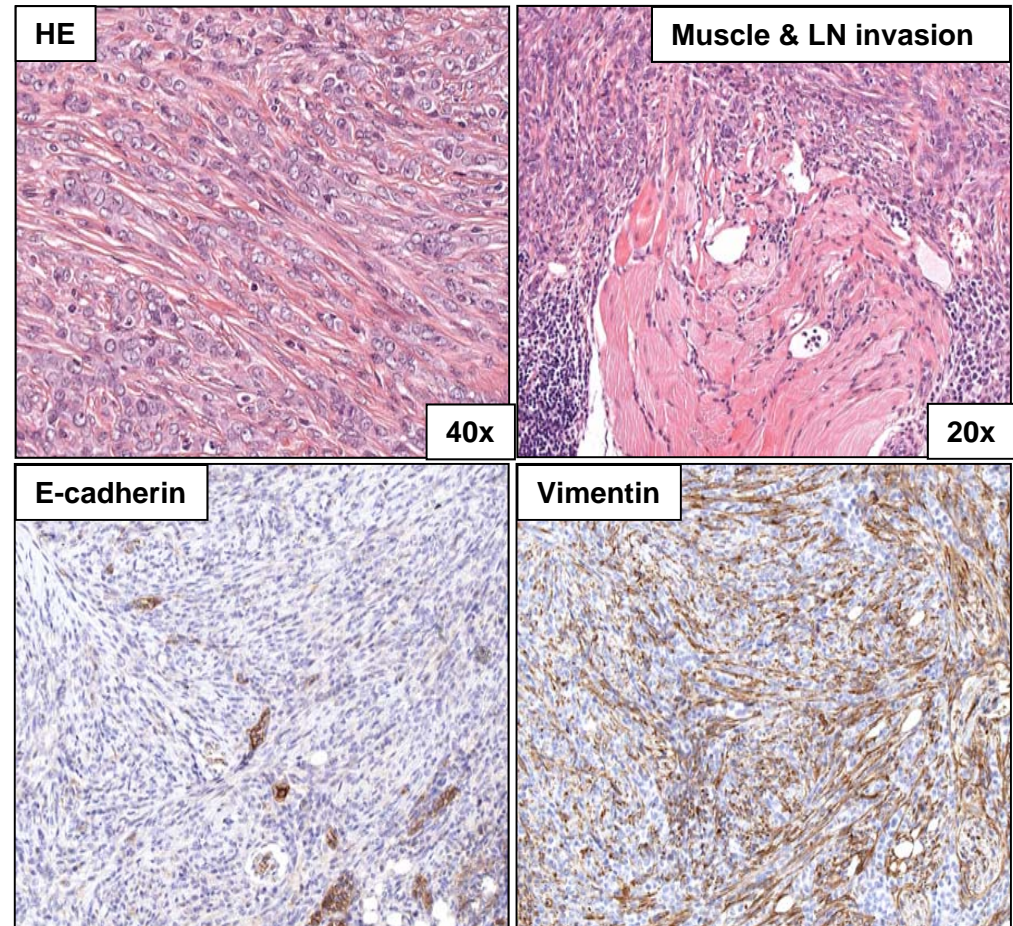
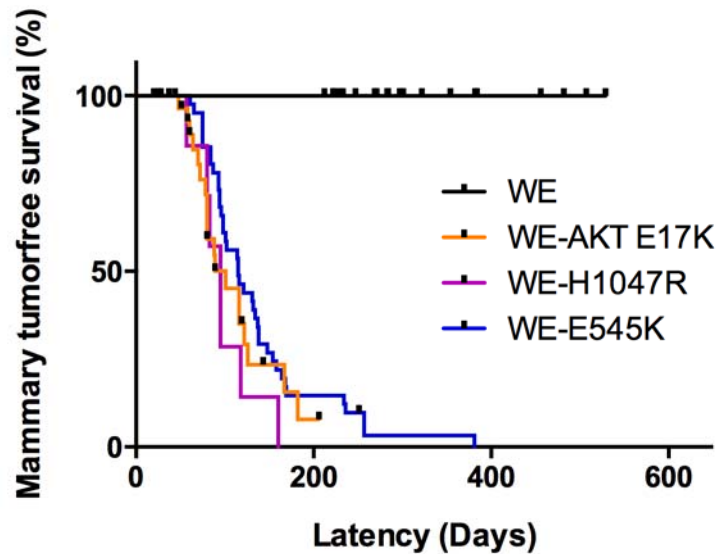
Modeling ILC by E-cadherin loss and mutant PIK3CA/AKT expression



- GEMM-ESC strategy:** rapid generation of novel mouse models using embryonic stem cells (ESCs) from existing GEMMs



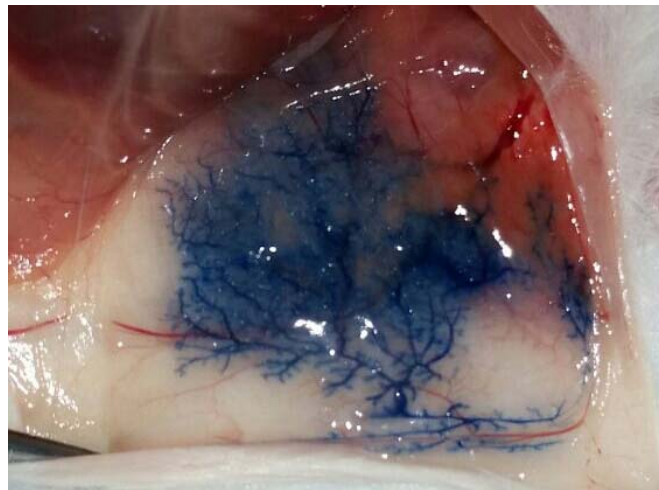
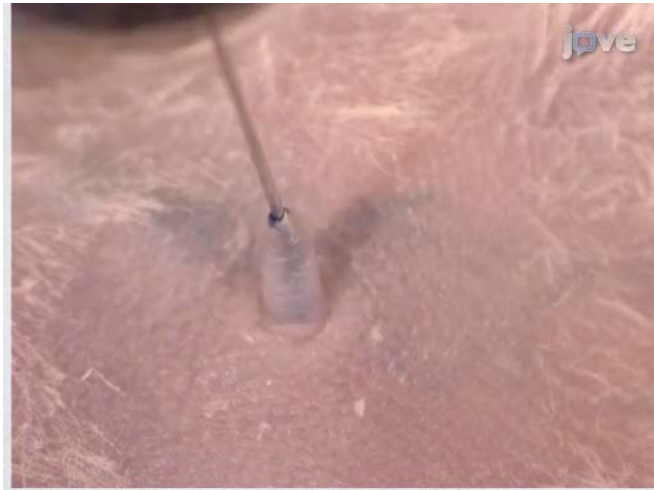
Modeling ILC by E-cadherin loss and mutant PIK3CA/AKT expression



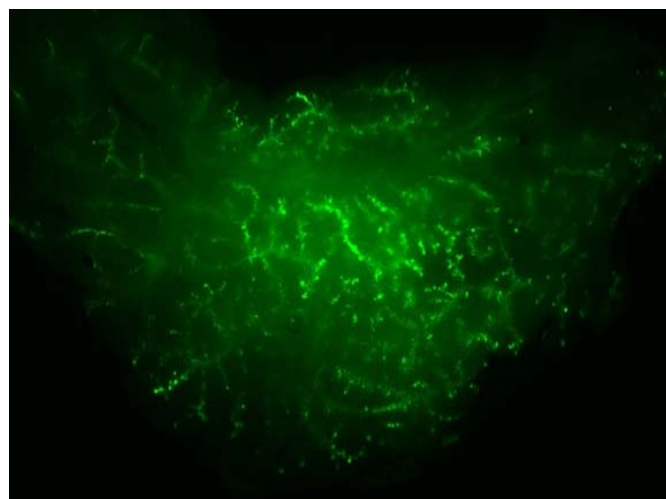
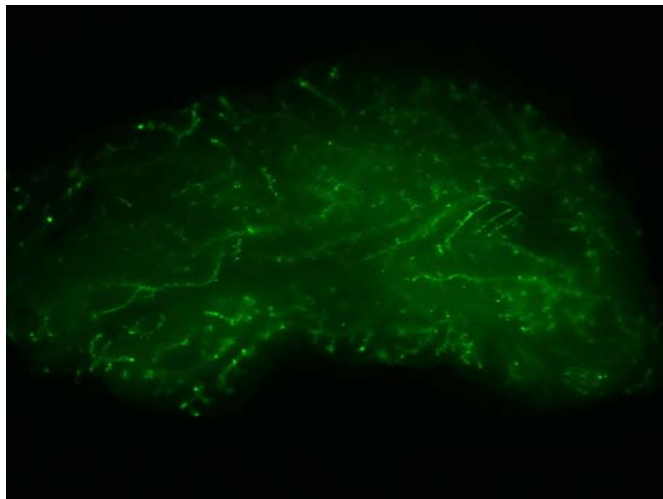
Non-germline GEMMs of invasive lobular carcinoma



- Set up of intraductal injections



Evans blue

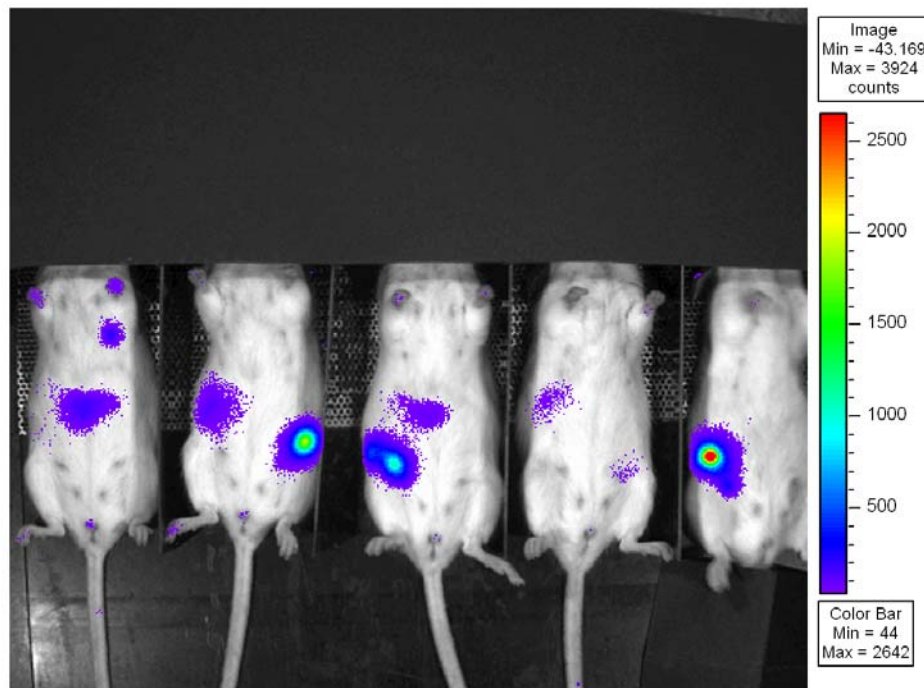


Lenti-GFP

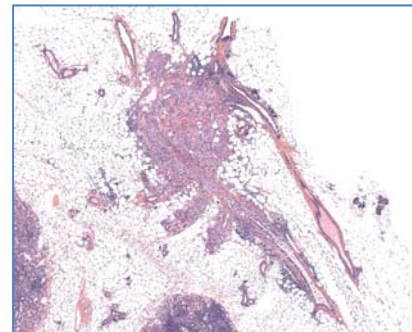
Non-germline GEMMs of invasive lobular carcinoma



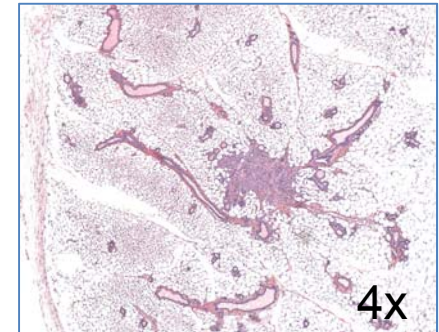
- Cre delivery by lentiviral intraductal injection in *Ecad^{F/F}; Inv-AKT-E17K* mice results in development of ILC lesions at 11 weeks



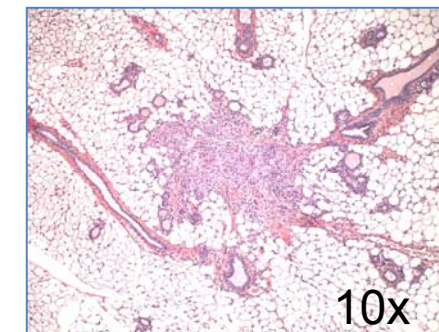
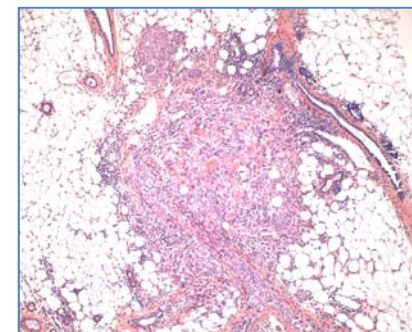
Lesion 1



Lesion 2



4x

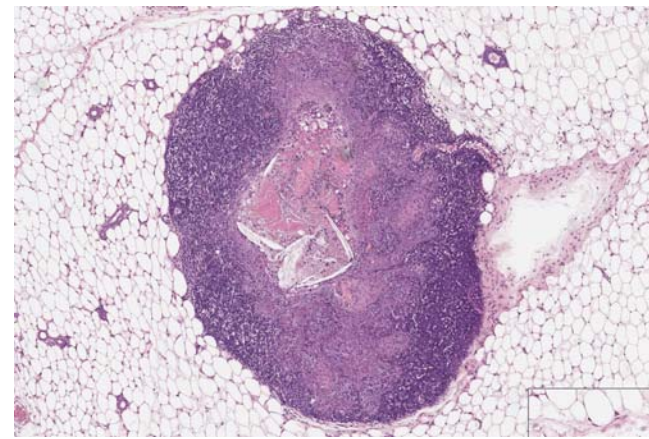
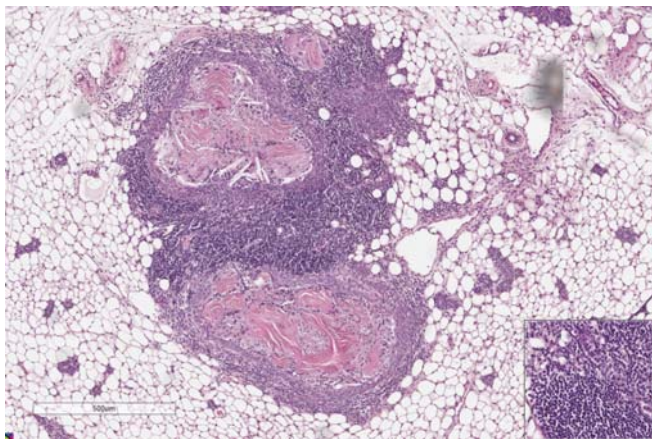
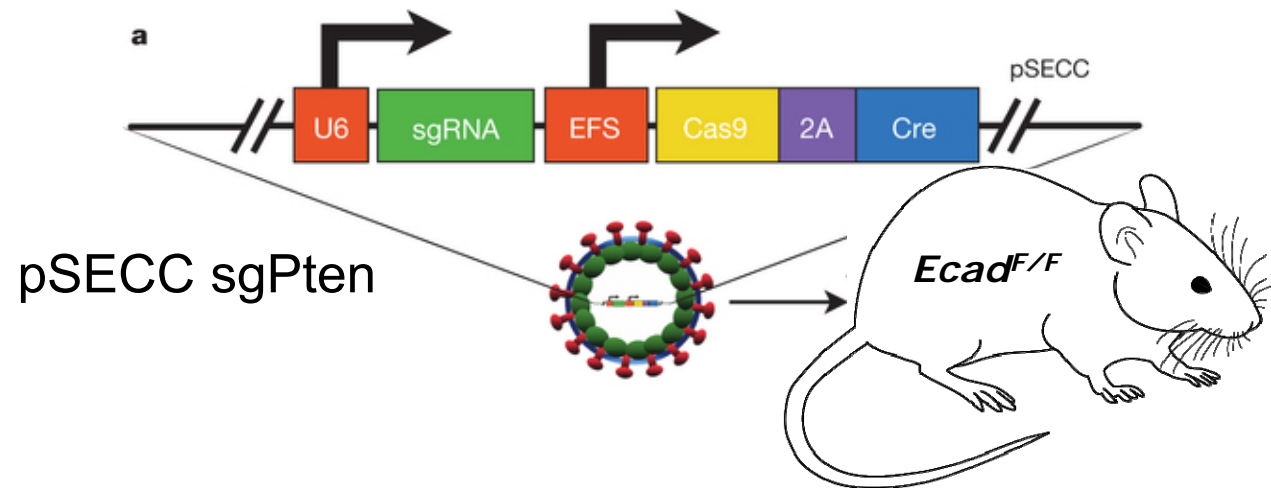


10x

Non-germline GEMMs of invasive lobular carcinoma



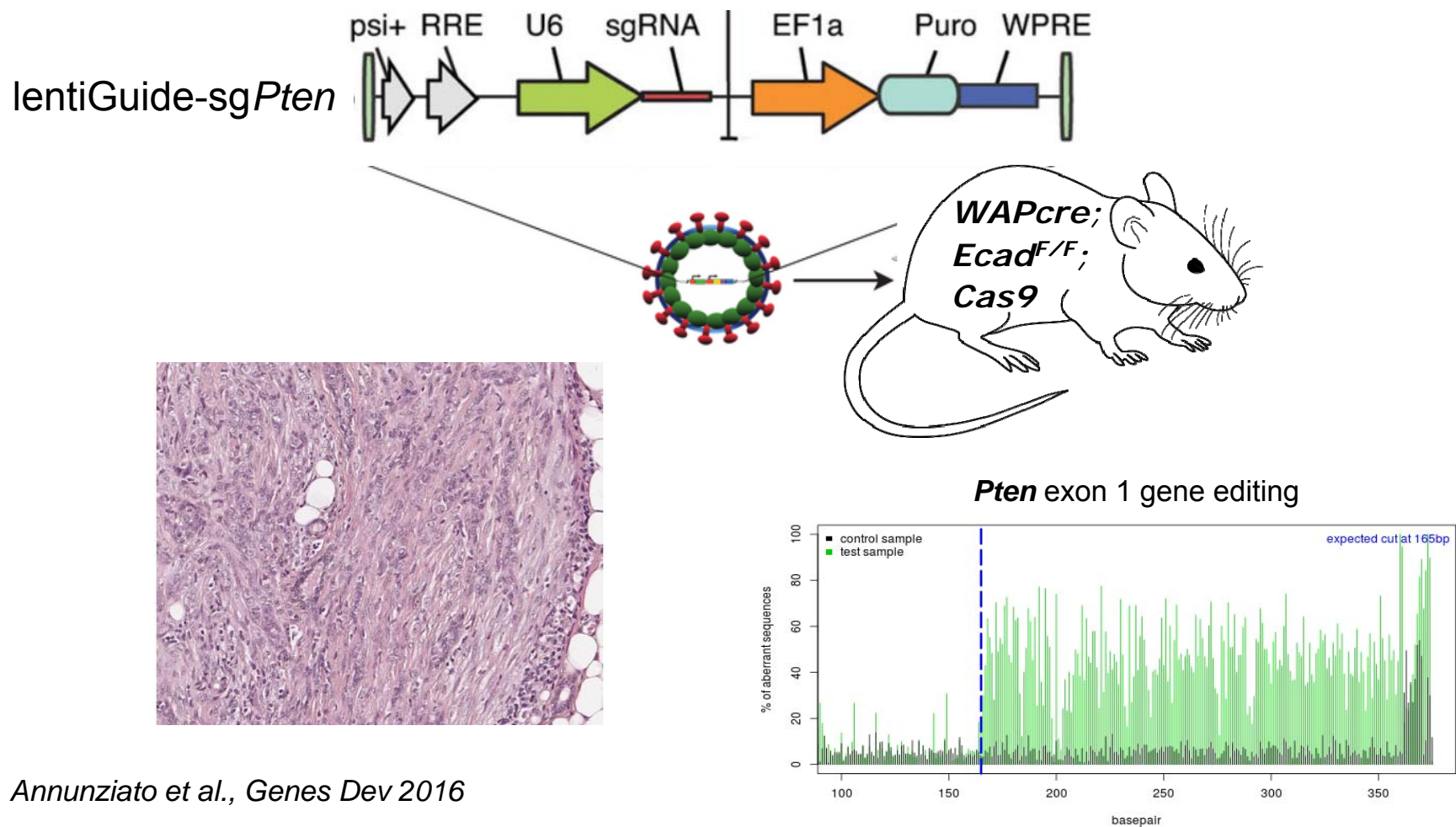
- Local delivery of CAS9 triggers an immune response



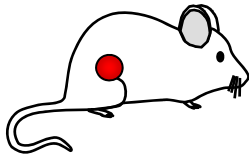
Non-germline GEMMs of invasive lobular carcinoma



- Intraductal injection of Lenti-*sgPten* in *WAPcre; Ecad^{F/F}; Inv-Cas9* mice results in ILCs at 25 weeks post-injection



GEMMs for BRCA1/2-associated breast cancer



K14cre;p53^{F/F}

→ tissue-specific
loss of p53



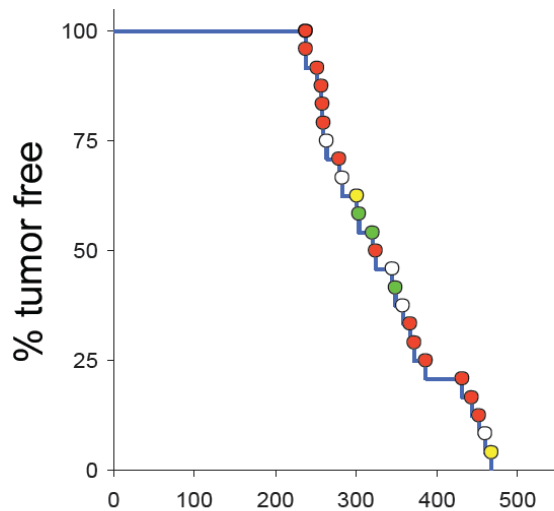
K14cre;Brca1^{F/F};p53^{F/F}

→ tissue-specific
loss of p53 + Brca1

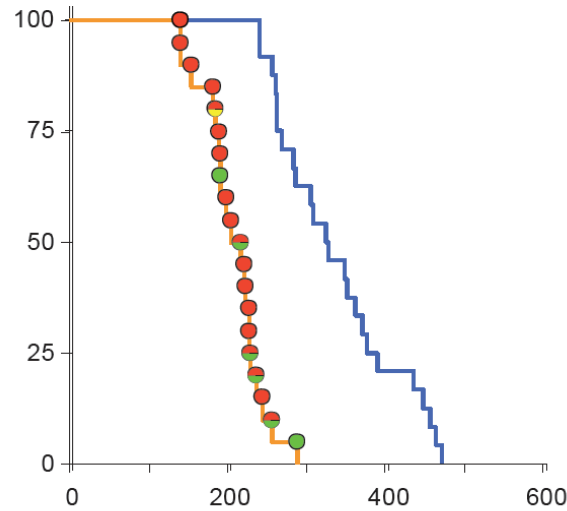


K14cre;Brca2^{F/F};p53^{F/F}

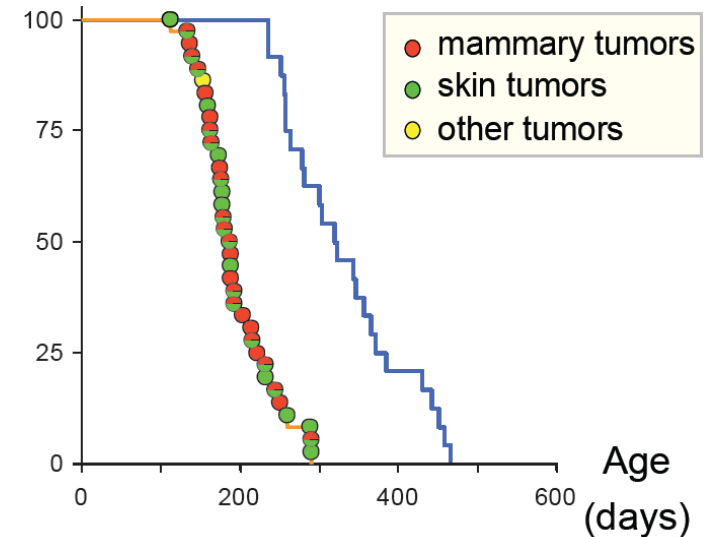
→ tissue-specific
loss of p53 + Brca2



$T_{50} = 290$ days

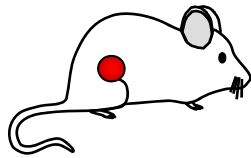


$T_{50} = 210$ days



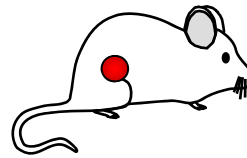
$T_{50} = 180$ days

GEMMs for BRCA1/2-associated breast cancer



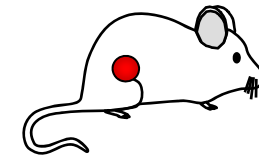
K14cre;p53^{F/F}

→ tissue-specific
loss of p53



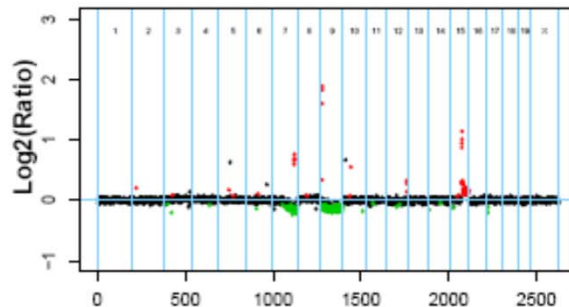
K14cre;Brca1^{F/F};p53^{F/F}

→ tissue-specific
loss of p53 + Brca1

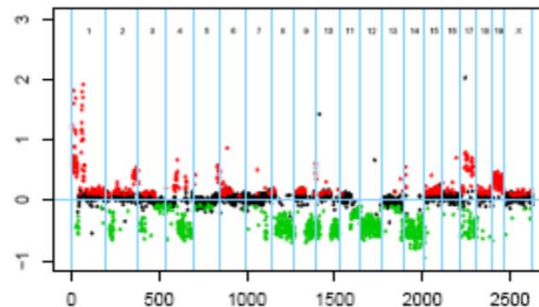


K14cre;Brca2^{F/F};p53^{F/F}

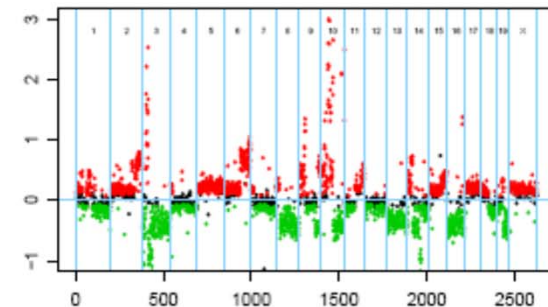
→ tissue-specific
loss of p53 + Brca2



p53^{-/-}
(BRCA-proficient)



Brca1^{-/-};p53^{-/-}
(BRCA1-null)

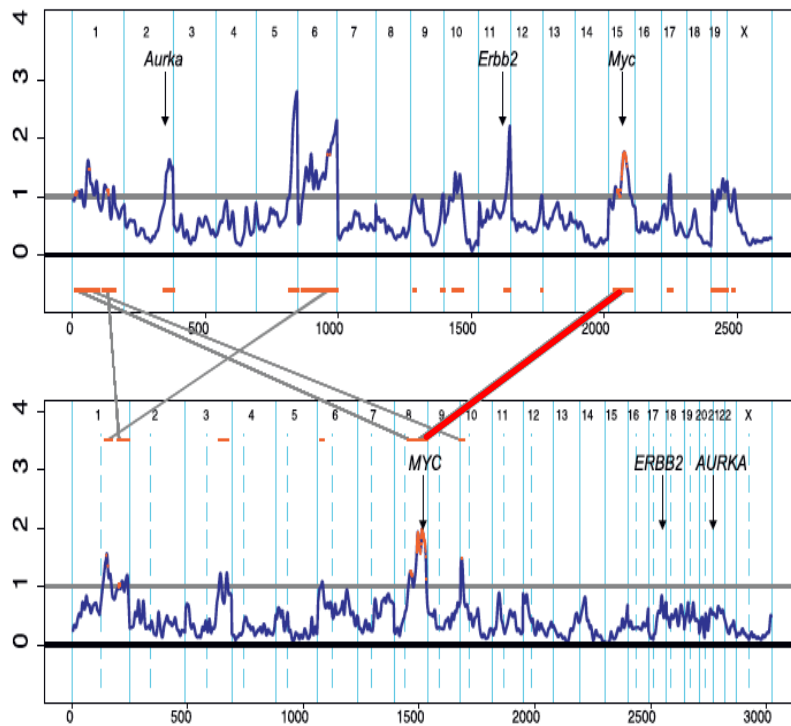


Brca2^{-/-};p53^{-/-}
(BRCA2-null)

Cross-species analyses of recurrent CNAs in mouse and human *BRCA1*-mutated breast tumors

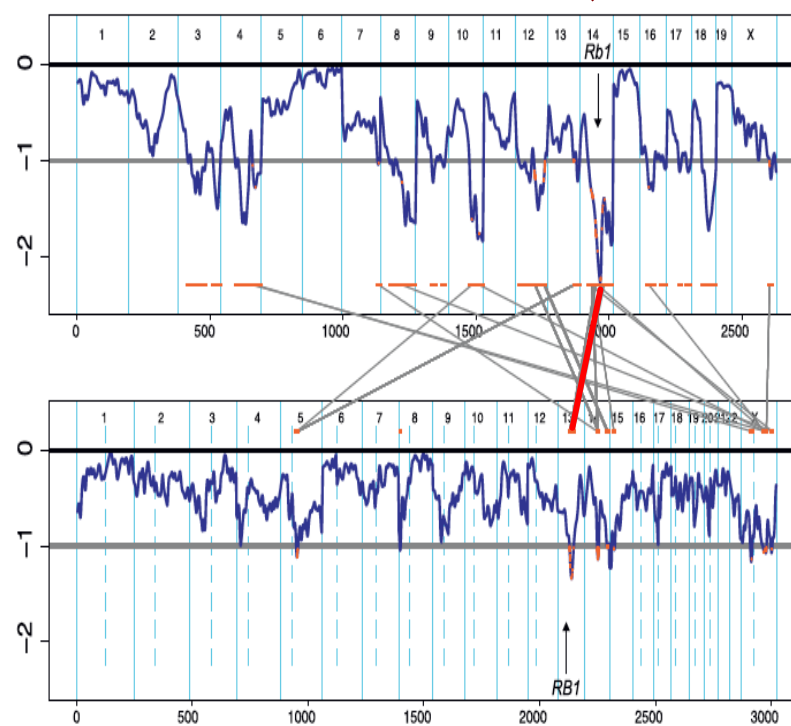


MYC



DNA copy number gains

RB1



DNA copy number losses



Mm

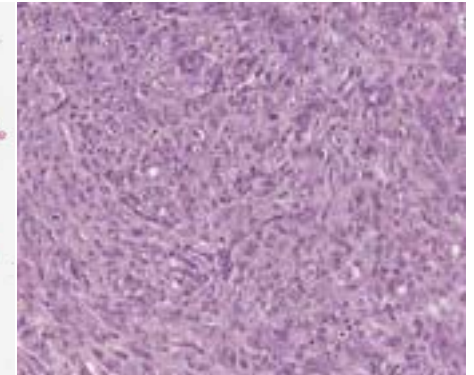
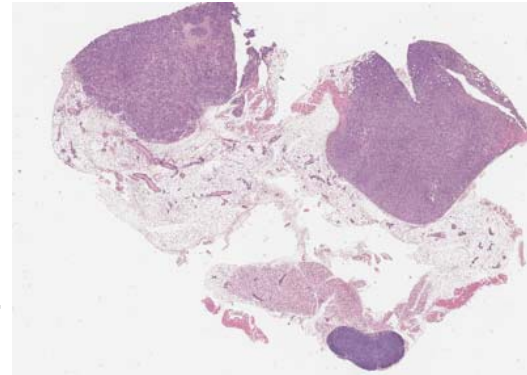
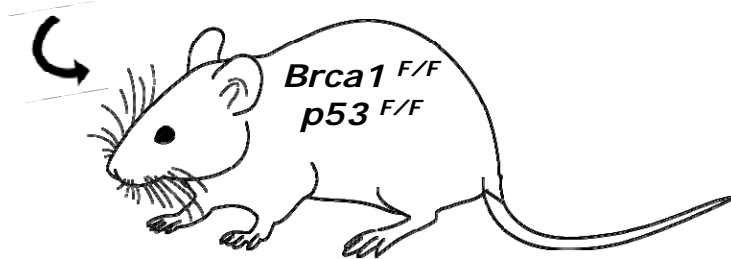


Hs

Non-germline GEMMs of triple-negative breast cancer

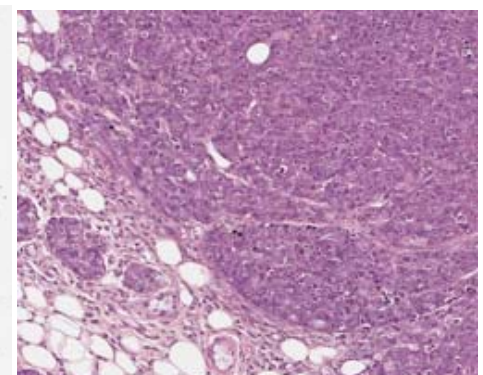
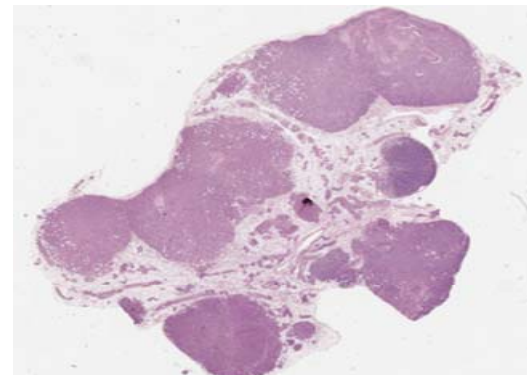
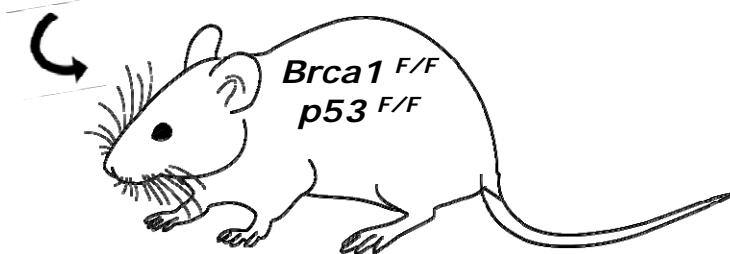


Intraductal
Lenti-Cre



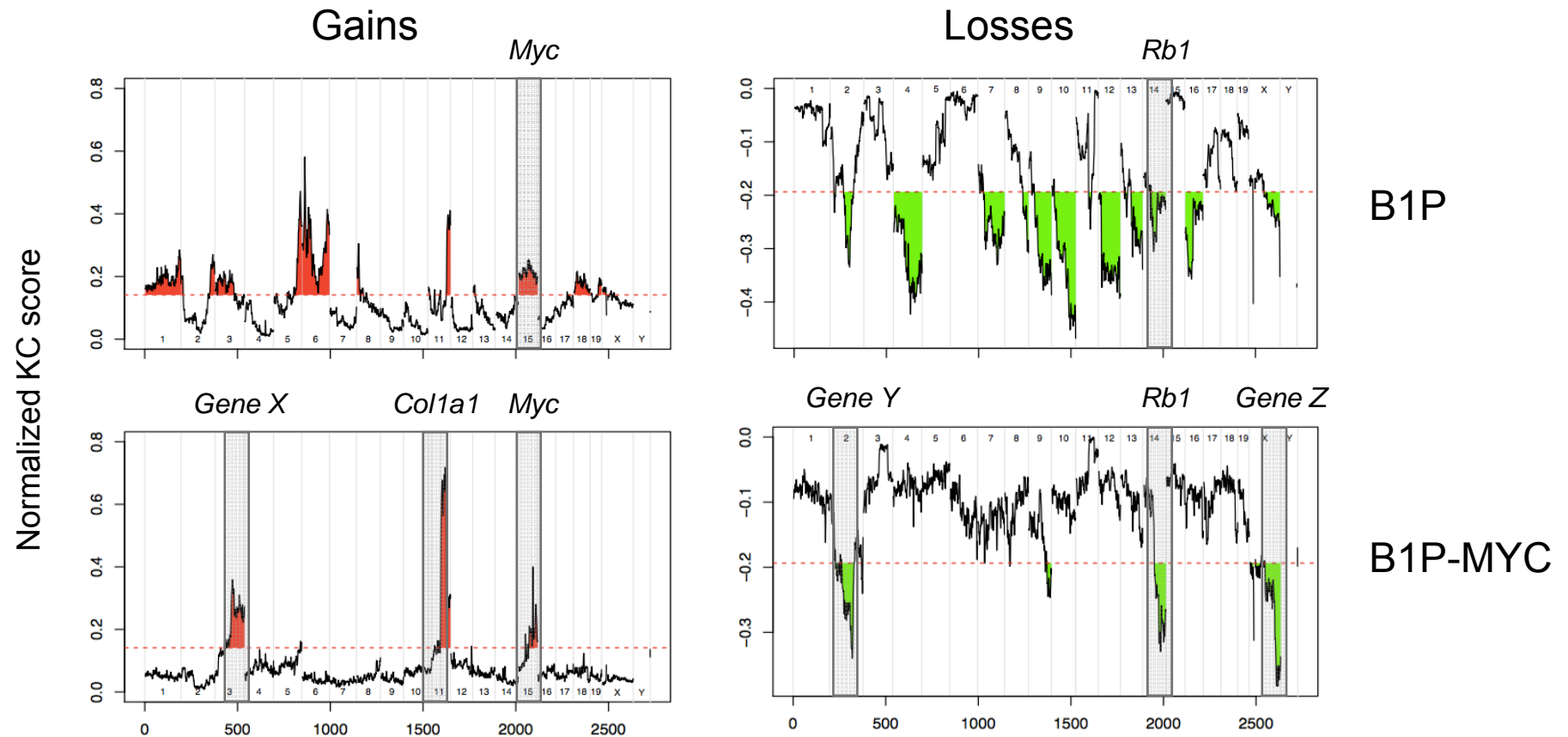
- TNBC formation in 100% of injected glands after 7 months

Intraductal
Lenti-Myc-T2A-Cre

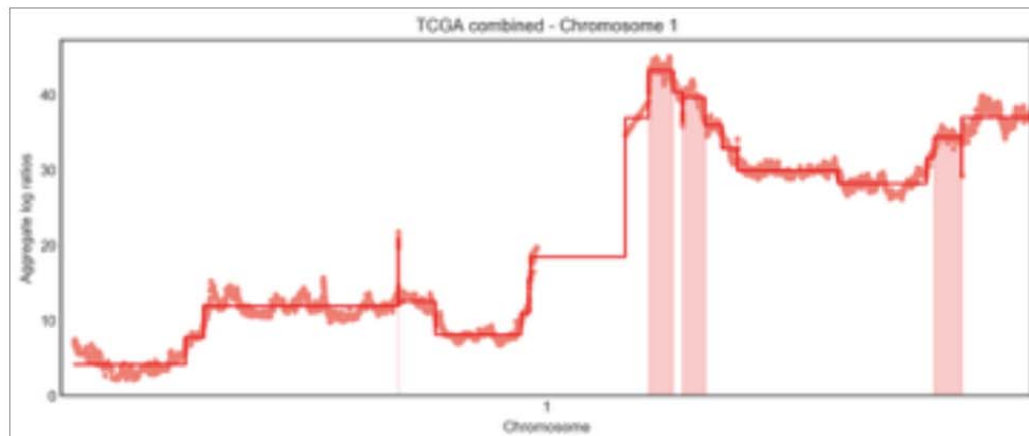
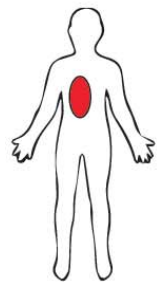
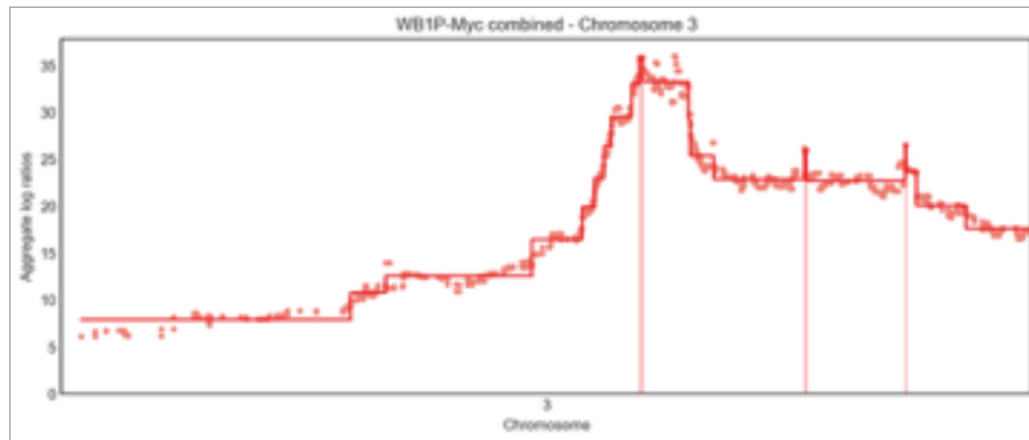


- TNBC formation in 100% of injected glands after 3.5 months

Recurrent CNAs in B1P-MYC tumors

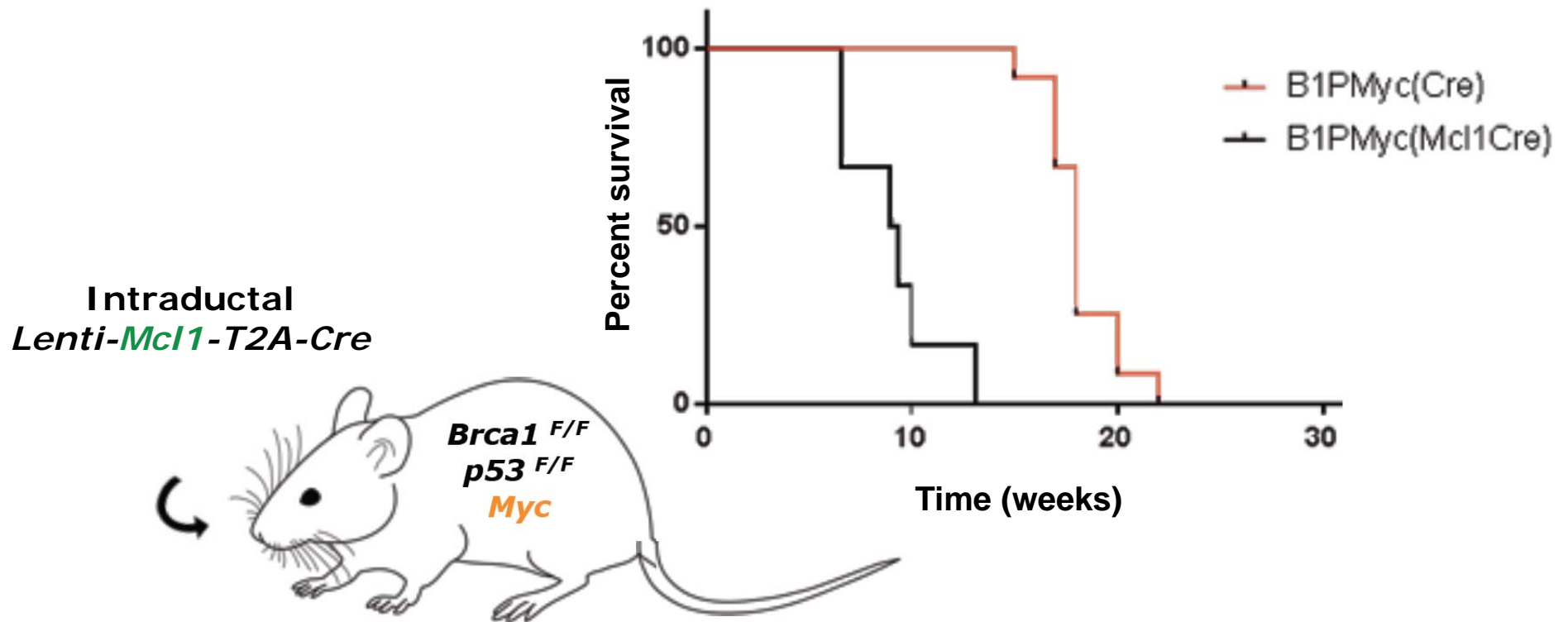


Comparative oncogenomics identifies Mcl1 as candidate driver in WB1P-MYC tumors



Gene	Correlation with expression
Tars2	0,524131741
Setdb1	0,425751026
Gm128	0,415573711
Bnpl	0,408788834
Rprd2	0,388434203
Golph3l	0,317192996
Mcl1	0,290053488
Mllt11	0,283268611
Cers2	0,239166911
Arnt	0,222204719
Gabpb2	0,201850088

Validation of MCL1 in BRCA1-associated breast cancer



ARTICLE

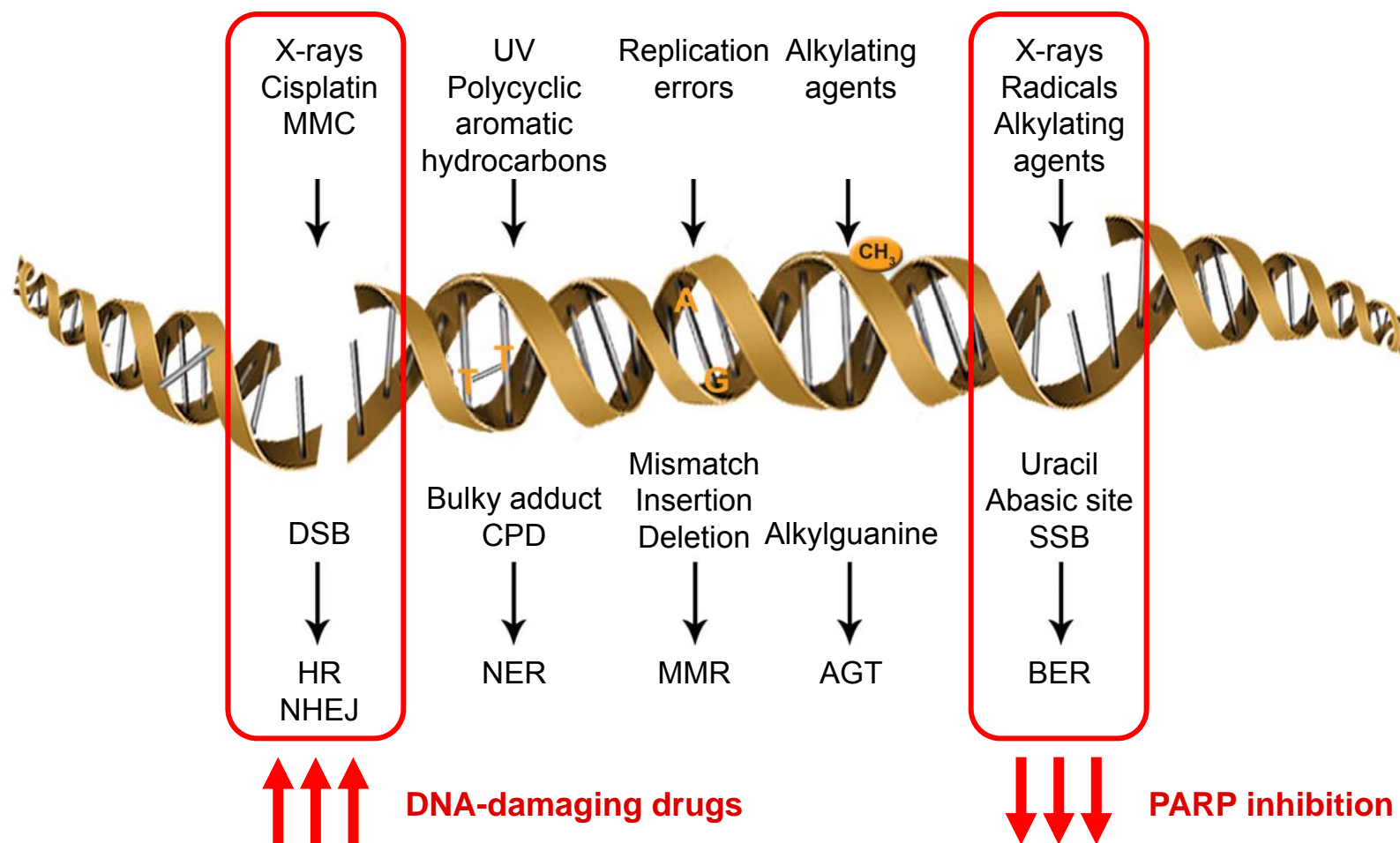
doi:10.1038/nature19830

The MCL1 inhibitor S63845 is tolerable and effective in diverse cancer models

Annunziato *et al.*, in prep.

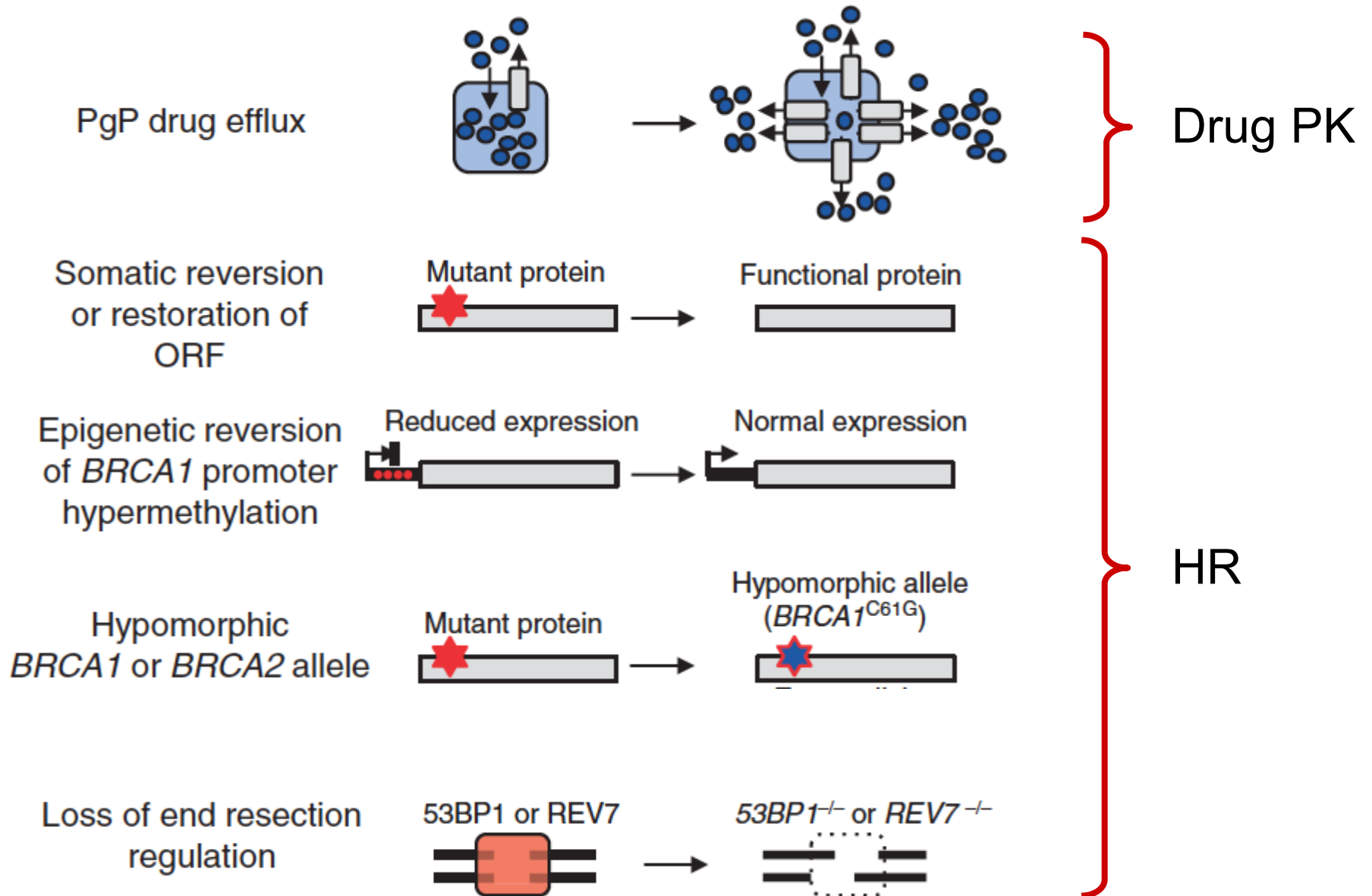
Kotschy *et al.*, Nature 2016; 538:477

Targeting HR deficiency in BRCA-mutated cancers



- Bryant et al, Nature 2005
- Farmer et al, Nature 2005

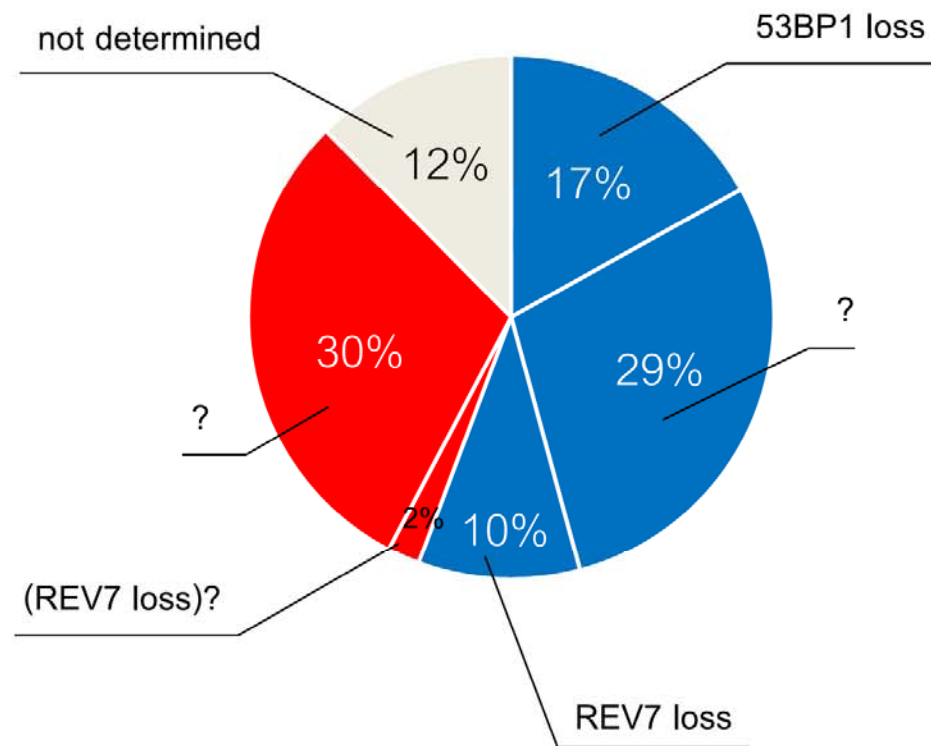
Known mechanisms of therapy resistance



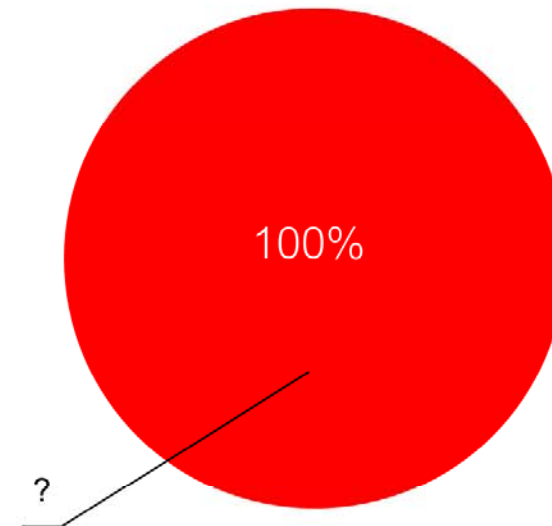
A large fraction of BRCA-deficient tumors may acquire therapy resistance without HR restoration



BRCA1-deficient tumors



BRCA2-deficient tumors



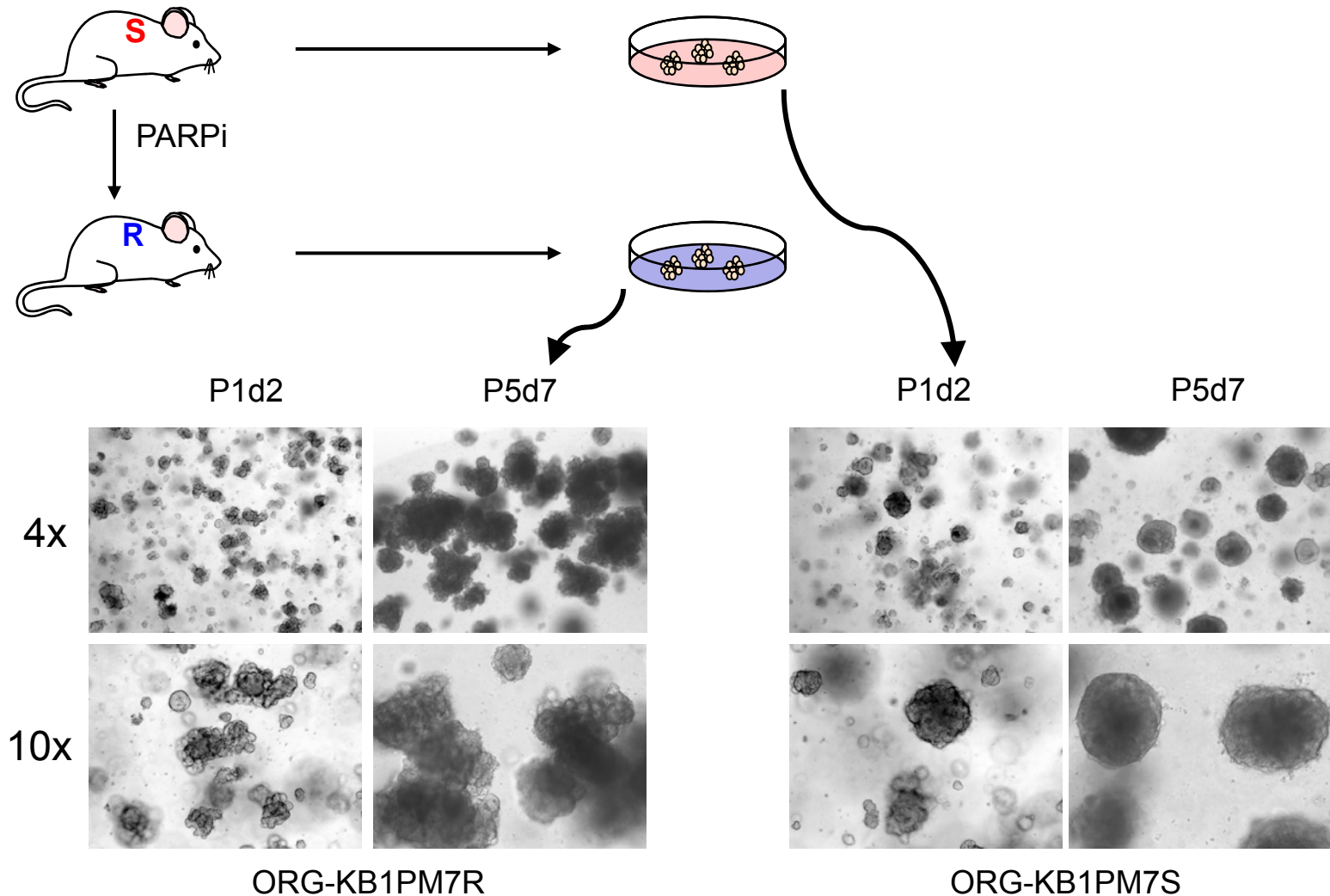
RAD51 foci formation status:

- negative
- positive
- not determined

Organoid models of BRCA-deficient breast cancer



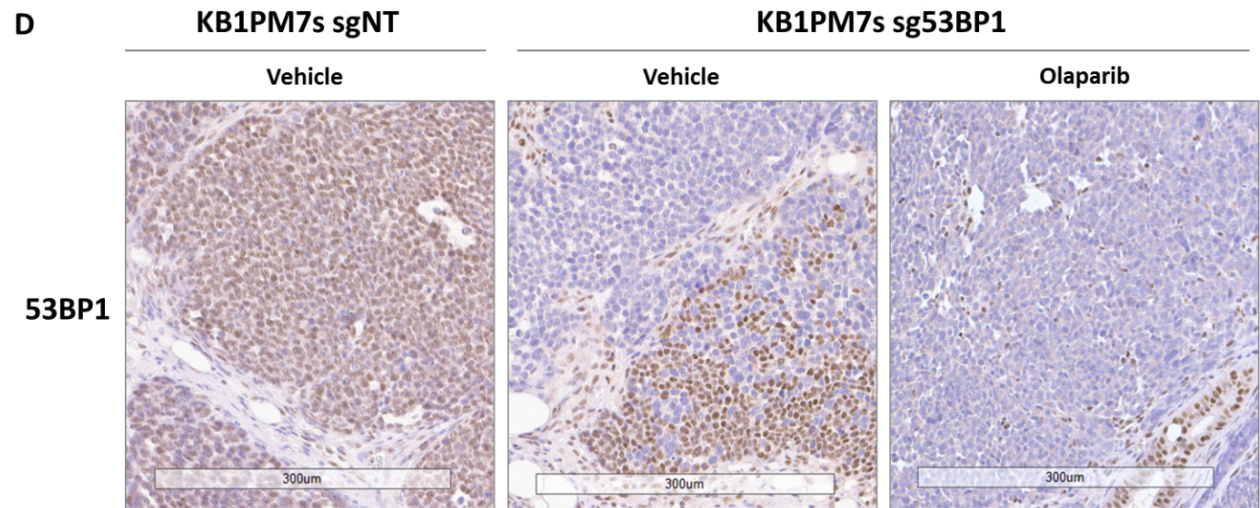
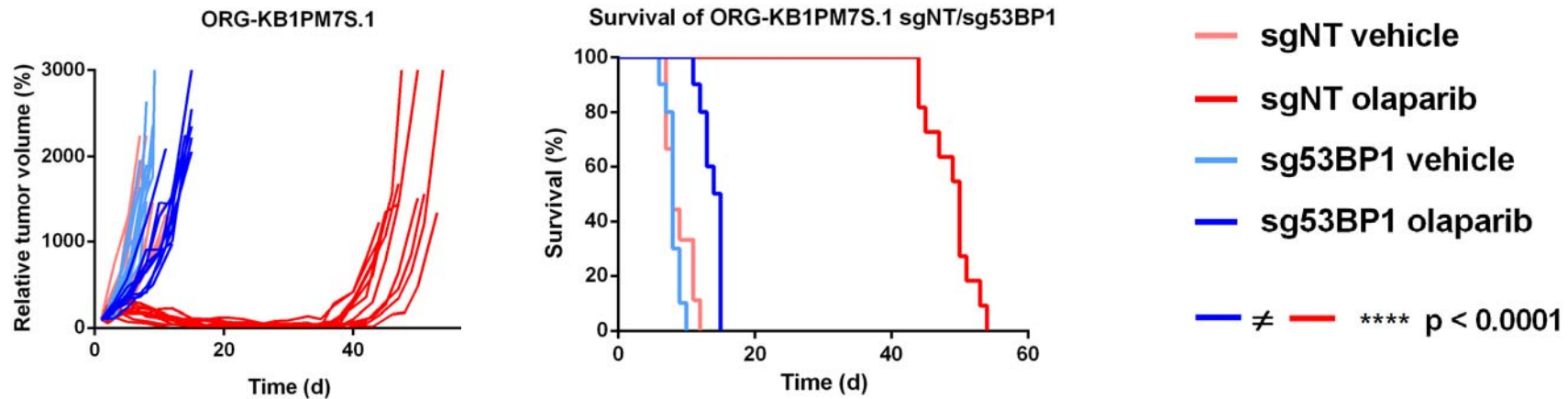
- BRCA-deficient tumor organoids can be readily established



Organoid models of BRCA-deficient breast cancer



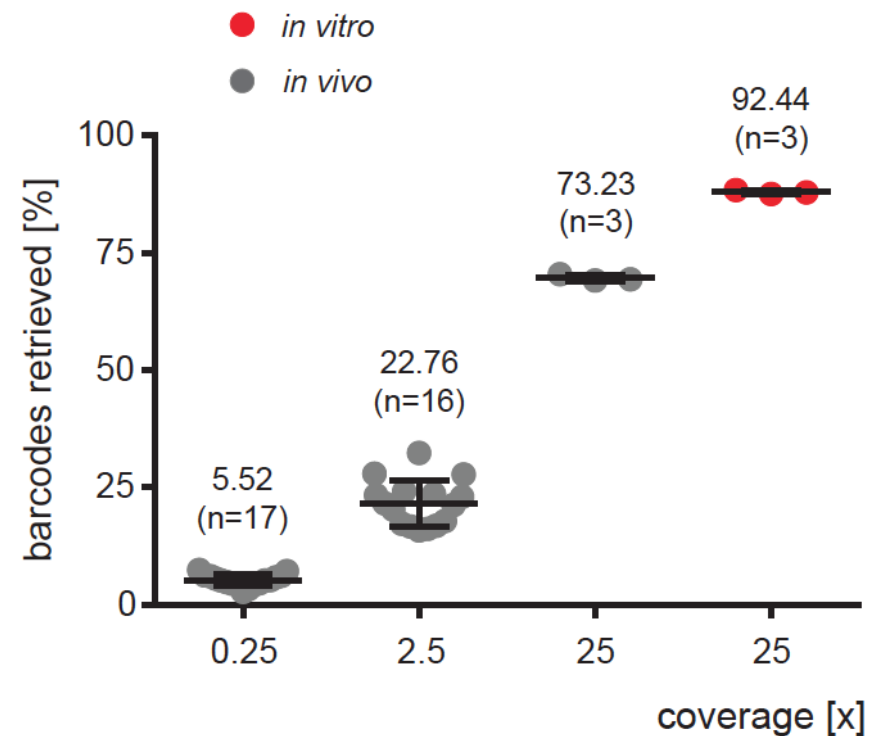
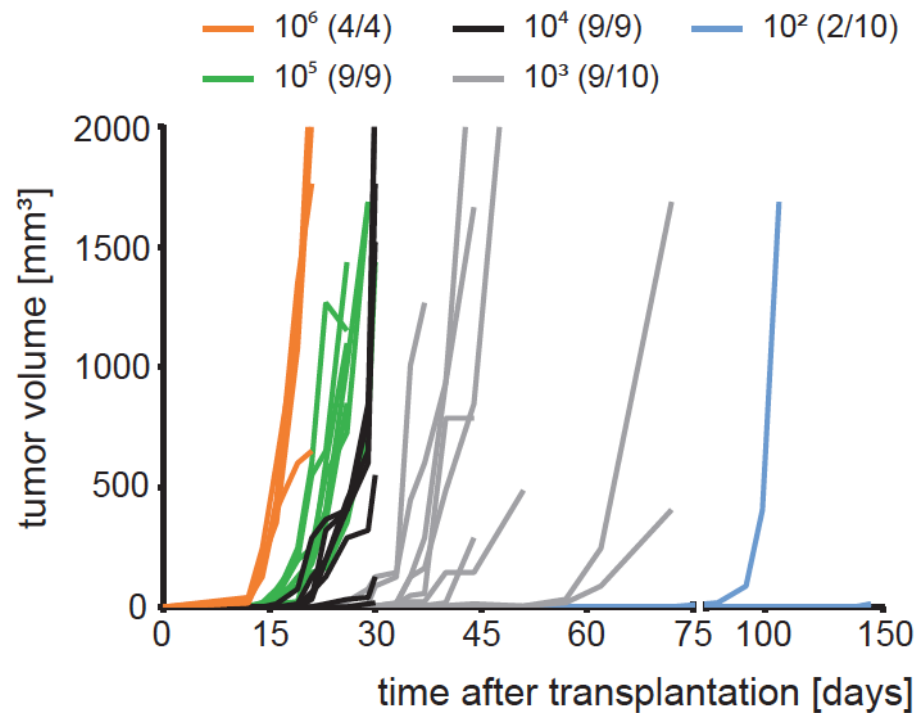
- Organoids can be used to test drug resistance candidates



Organoid models of BRCA-deficient breast cancer



- Organoids show high *in vivo* clonogenicity upon orthotopic transplantation



GEMMs of human cancer

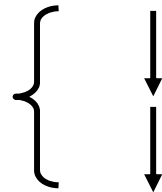


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Cancer gene validation



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Tumors

Drug target validation
Therapeutic intervention

Minimal residual disease

Relapses

Therapeutic intervention

Resistance mechanisms

Resistance

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