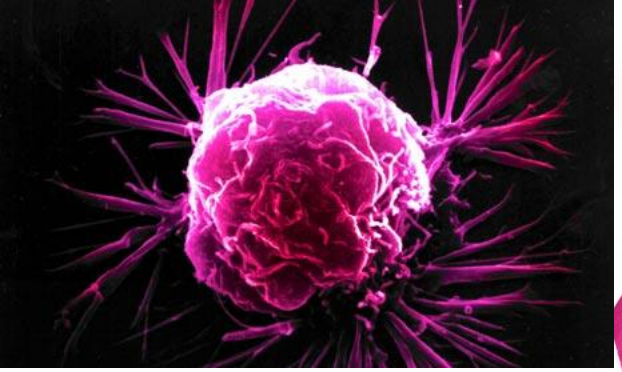

DEAD-BOX RNA HELICASE DP103 REGULATED SUMO/ACETYLATION SWITCH OF P53 DETERMINES RESPONSE TO DOCETAXEL IN ERα-POSITIVE BREAST CANCER

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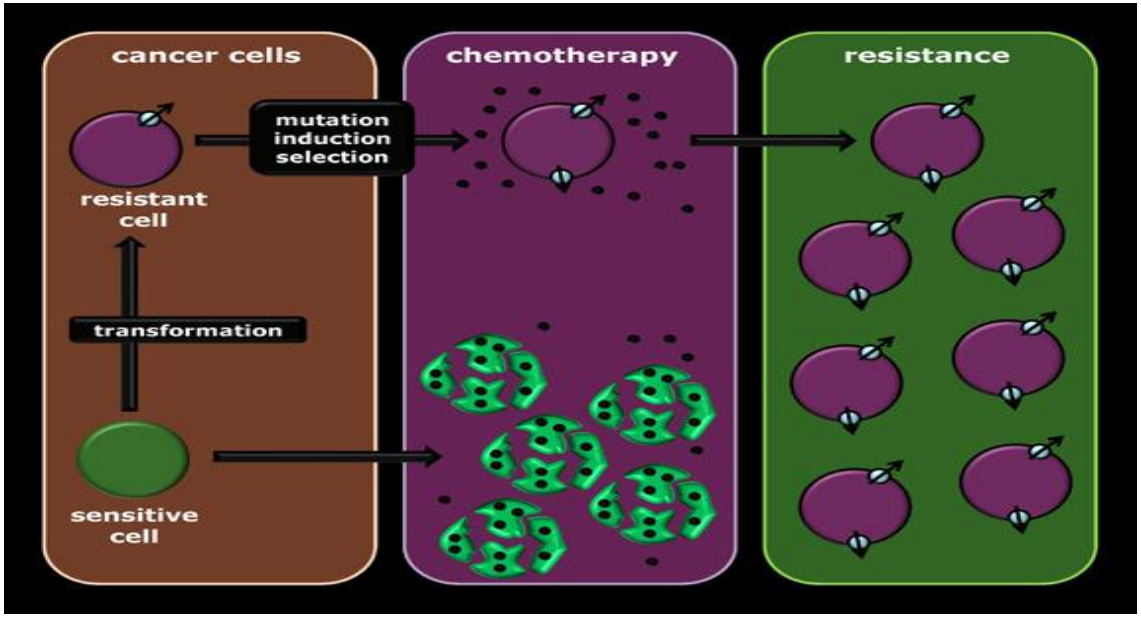
Chemoresistance
'MAN PROPOSES : TUMOR DISPOSES'



- Accounts for over 90% of treatment failures in patients with metastatic breast cancer (Longley et al., 2005)
- Time-to-Progression (**TTP**) of **6-10 months** (Cortes et al., 2007)

Popular Mechanisms Behind Docetaxel Resistance

β-tubulin gene mutations or differential expression

Suppression of pro-apoptotic genes (p53, Bax, Caspases)

Multi-Drug Resistant phenotype (PgP)

Activation of survival genes (PI3K/Akt, Bcl2)

Increased cellular drug detoxification

None has been successfully employed in the clinic to aid as predictive marker of docetaxel-response and -resistance (Camerini et a., 2011)

In Pursuit of New Biomarkers.....

Breast Cancer

Response to Docetaxel

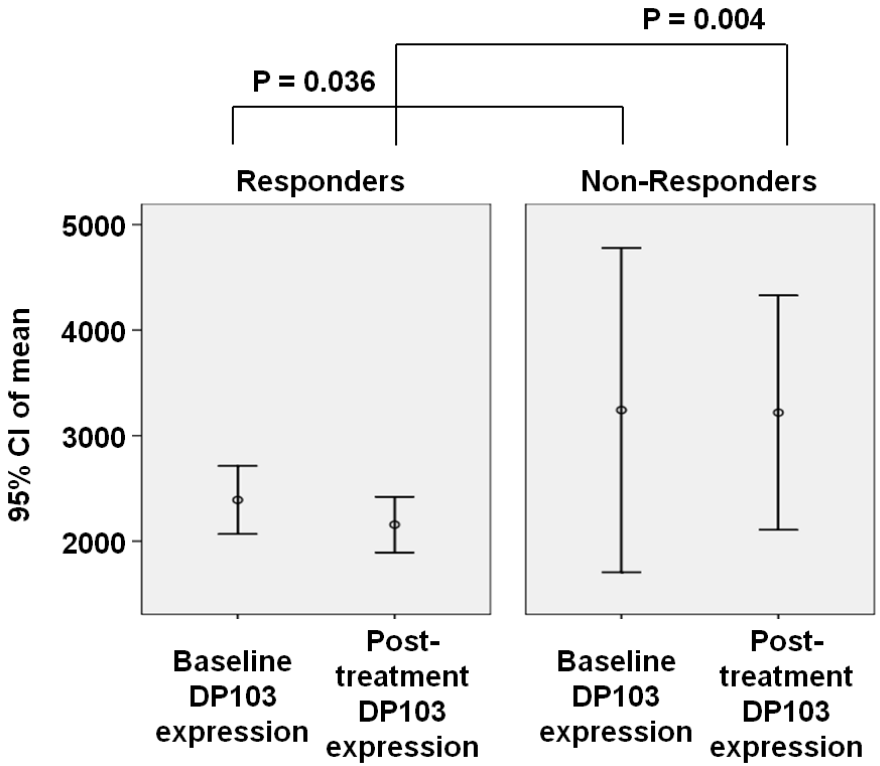
NUS National University of Singapore

CSI SINGAPORE

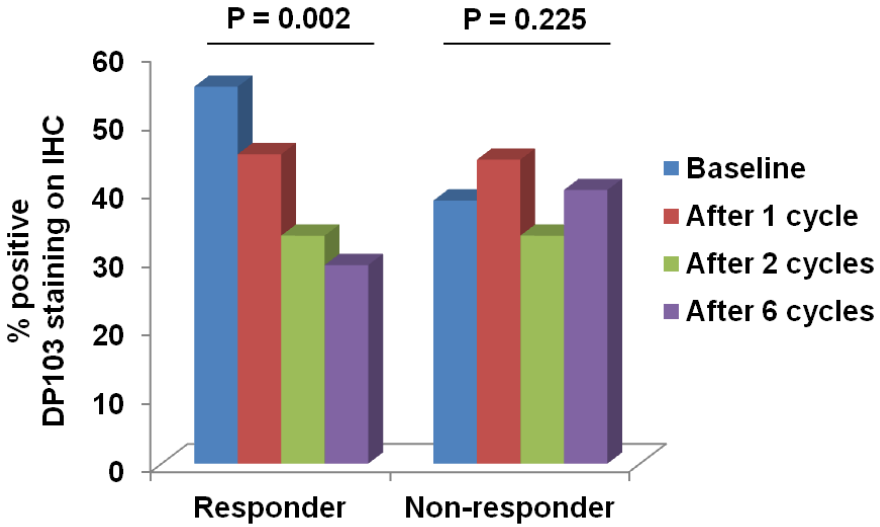
DEAD Box Protein, DP103: coming ALIVE in Cancer

- **Tumor-suppressor** in Hepatocellular Carcinoma (Zender et al., 2008, Takata et al., 2012)
- **Upregulated** in Mantle-Cell Lymphomas (Ghobrial et al., 2005)
- Increases the **metastatic potential of breast cancer** cells through **activation of NFκB,** and being **regulated by NFκB** itself (Shin et al., 2014)

Clinical Responders exhibit a chemotherapy-induced decrease in DP103 expression

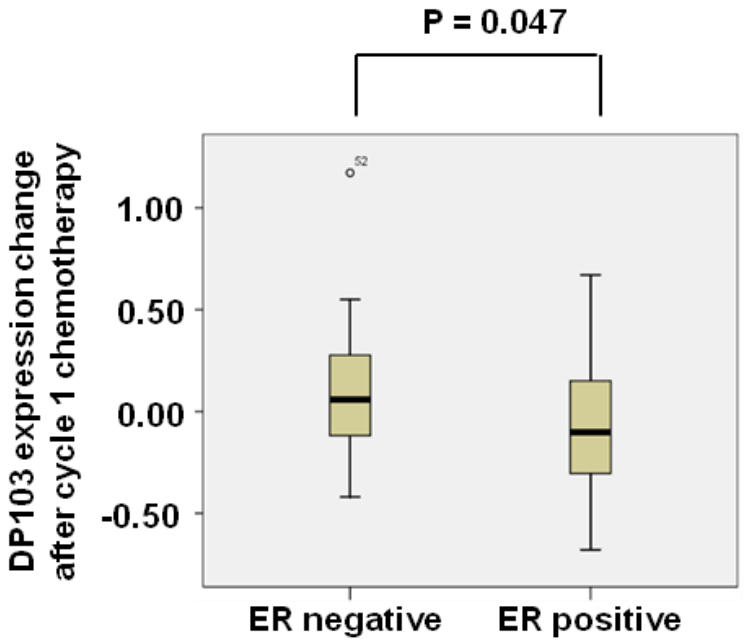


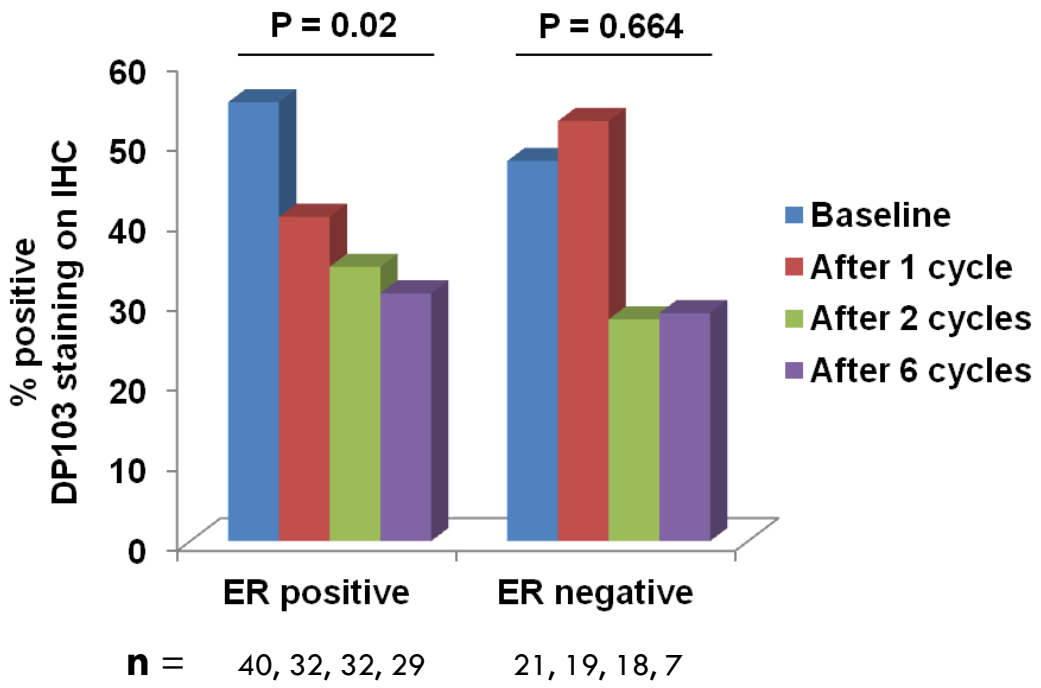
n = 54 48 11 8



n = 49, 42, 39, 31 13, 9, 12, 5

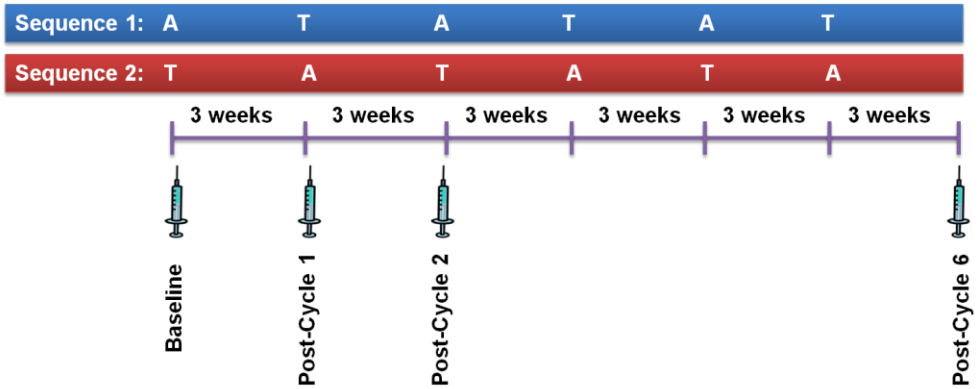
Chemotherapy negatively regulates DP103 expression in ER positive patients

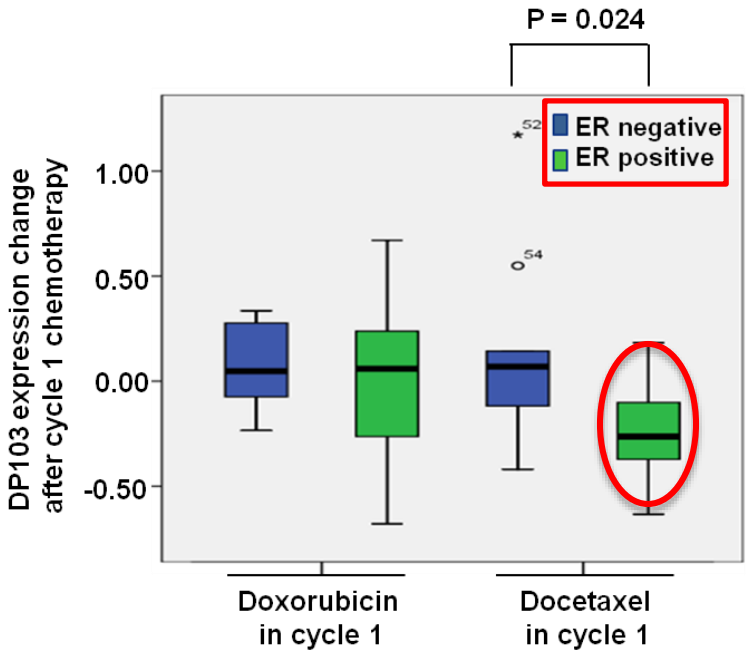




n = 40, 32, 32, 29 21, 19, 18, 7

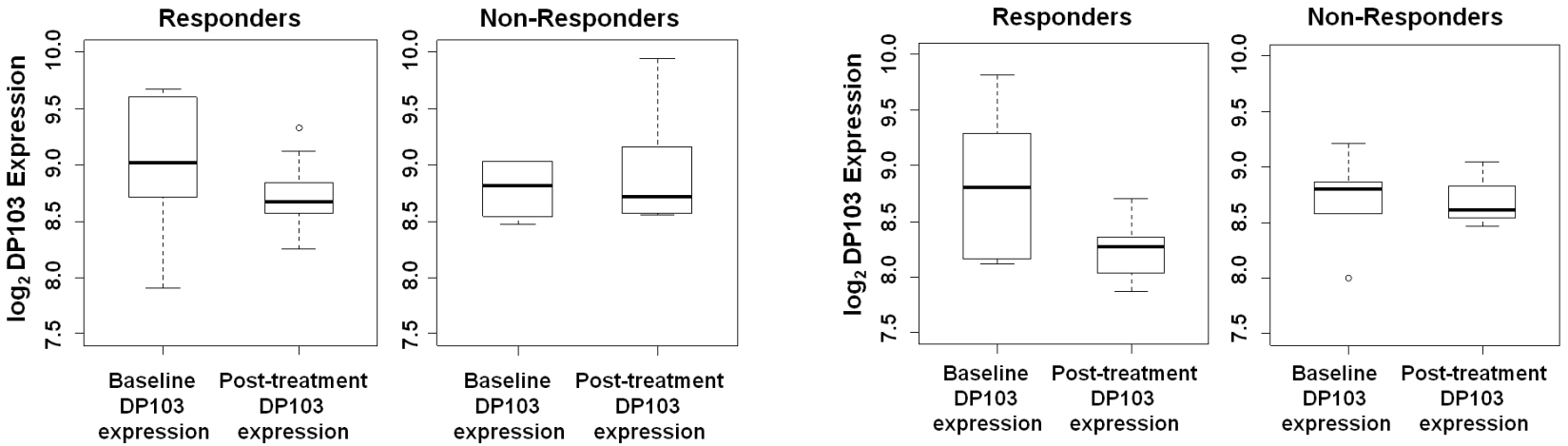
Docetaxel negatively regulates DP103 expression in ER positive patients





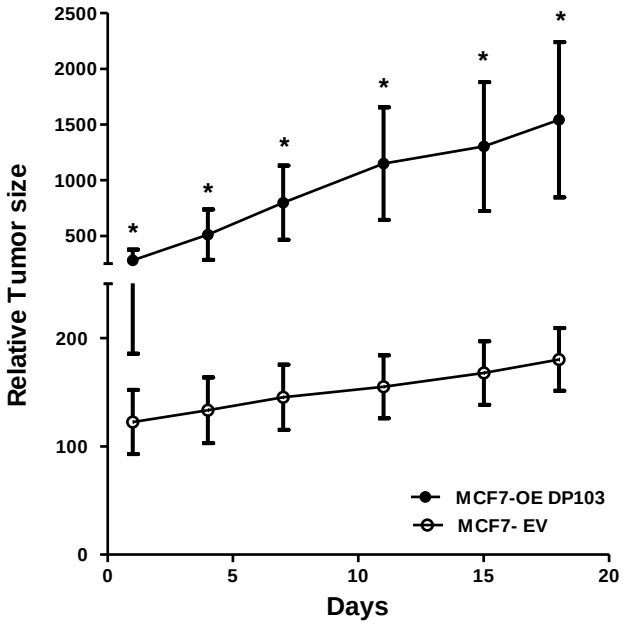
Docetaxel negatively regulates DP103 expression in ER positive patients

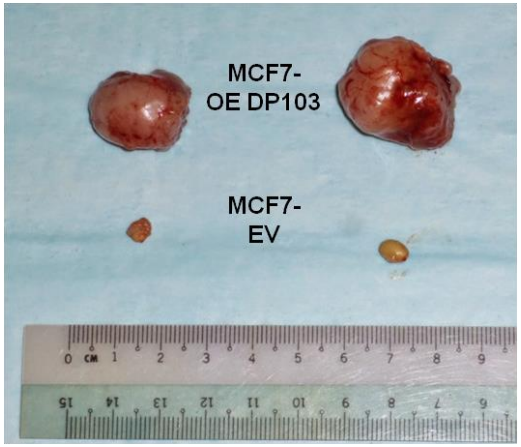
GEO gene expression data sets GSE21974 (Left) & GSE18728 (Right)

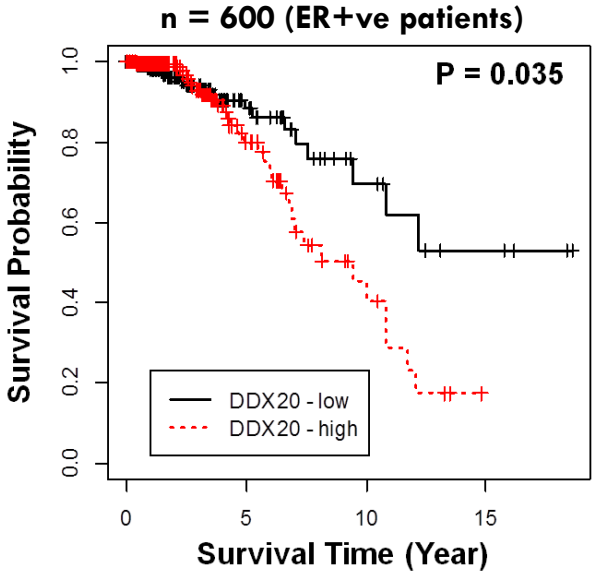


(n=31, p=0.028) **(n=14, p=0.98)** **(n=13, p=0.05)** **(n=8, p=0.96)**

DP103 over-expression increases tumor burden

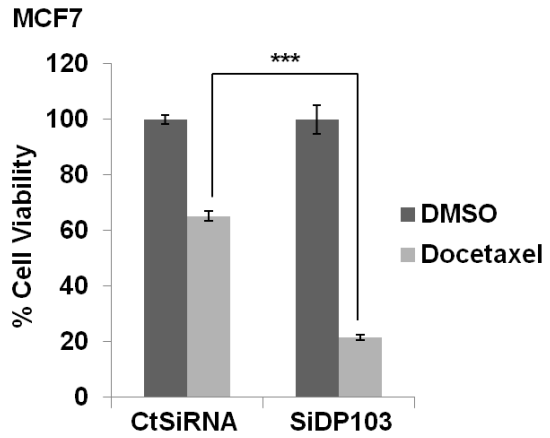


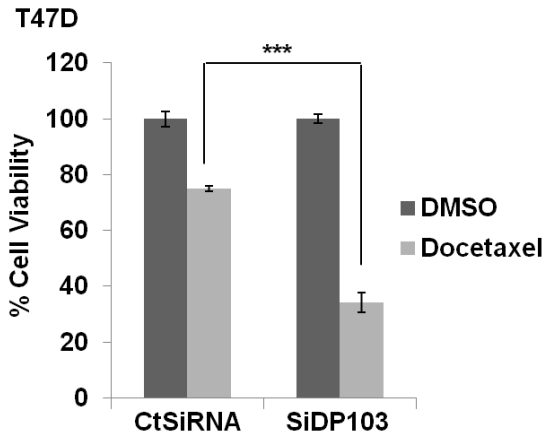


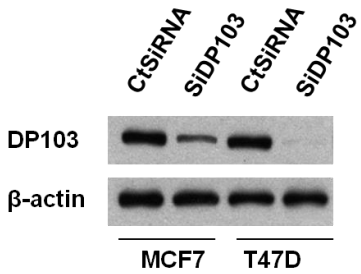


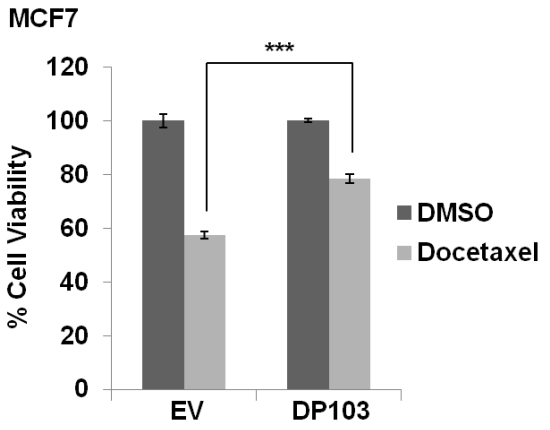
* denotes P value < 0.05

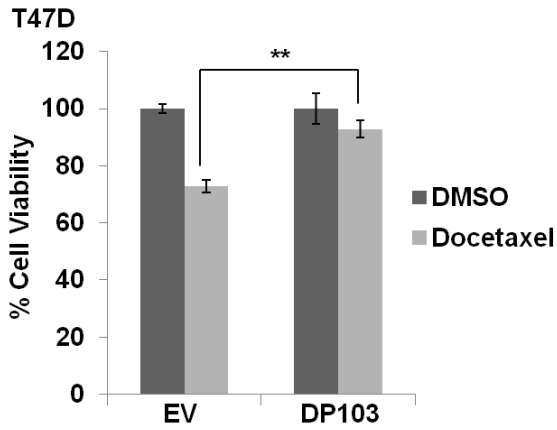
DP103 modulates docetaxel sensitivity

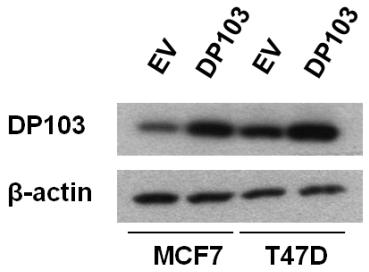






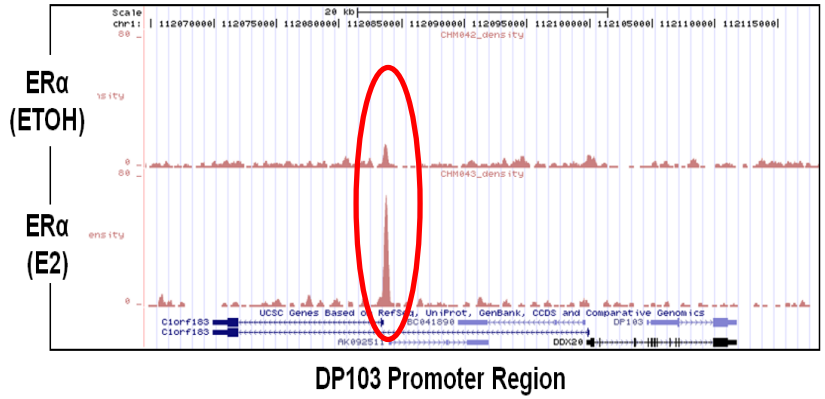


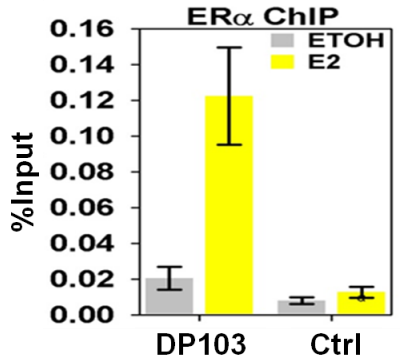


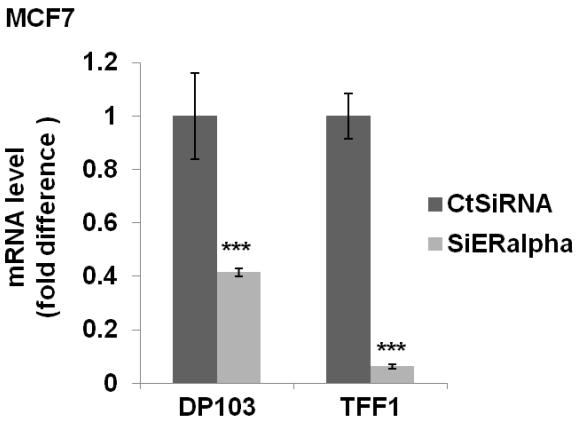


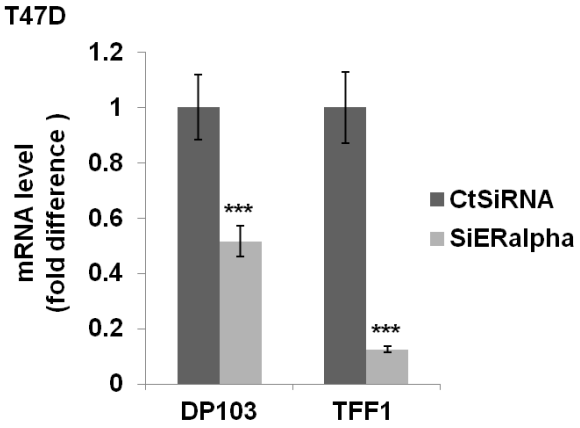
** denotes P value < 0.01, *** denotes P value < 0.001

ERα regulates DP103 transcriptionally

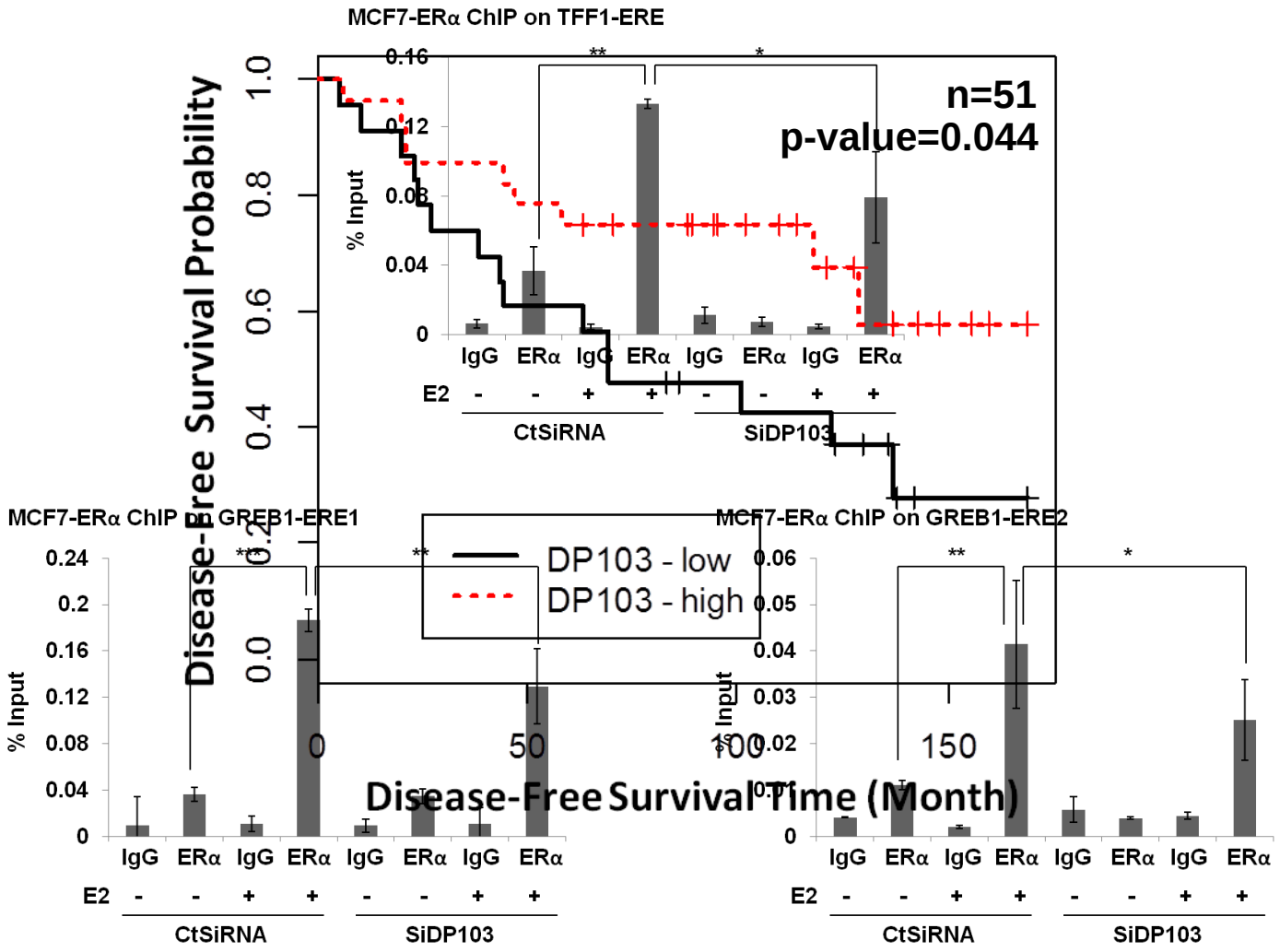






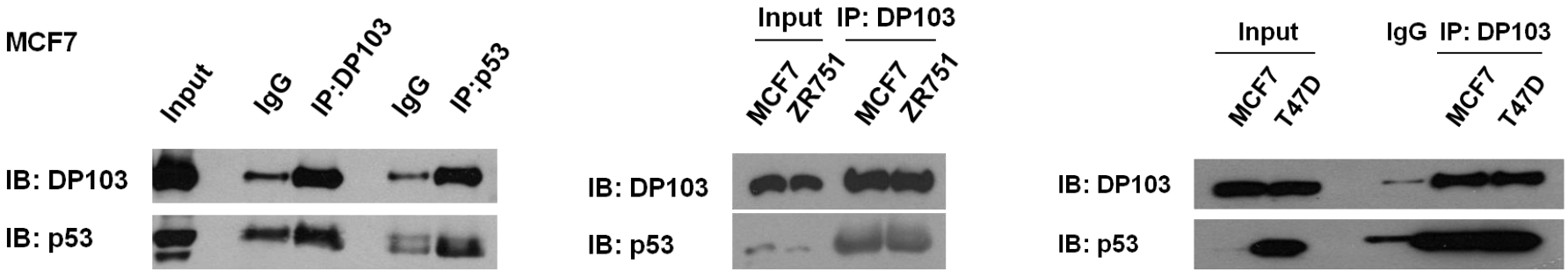


DP103 modulates recruitment of ERα to the promoter

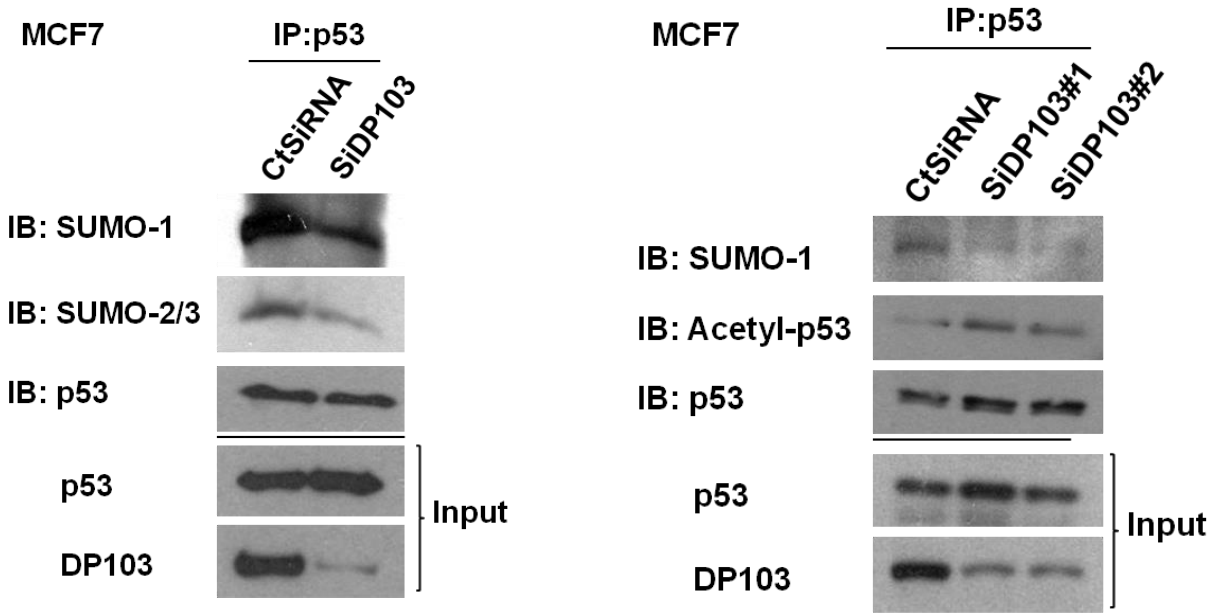


* denotes P value < 0.05, ** denotes P < 0.01, *** denotes P < 0.001

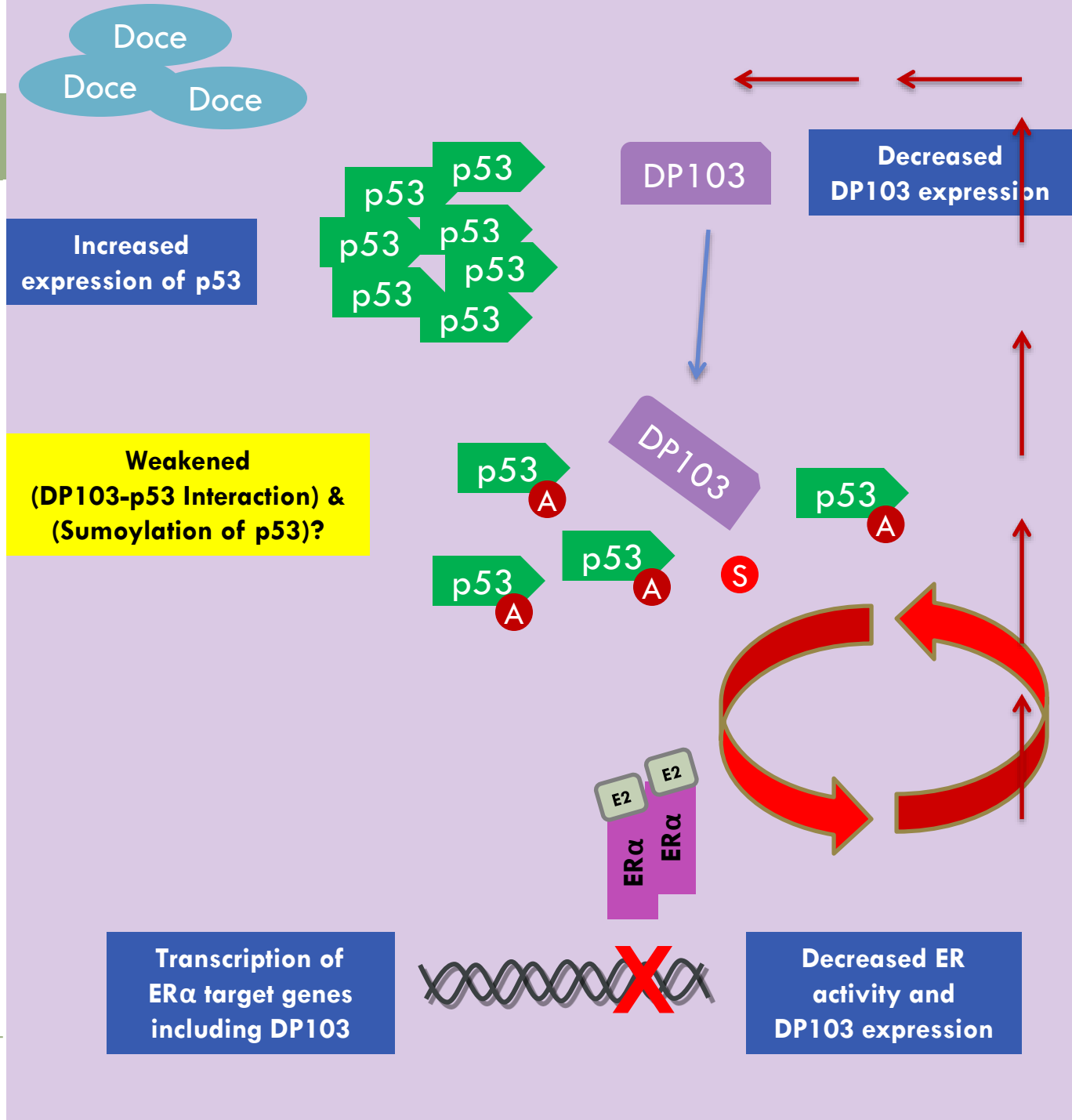
DP103 interacts with p53



DP103 modulates the switch between p53 sumoylation and acetylation



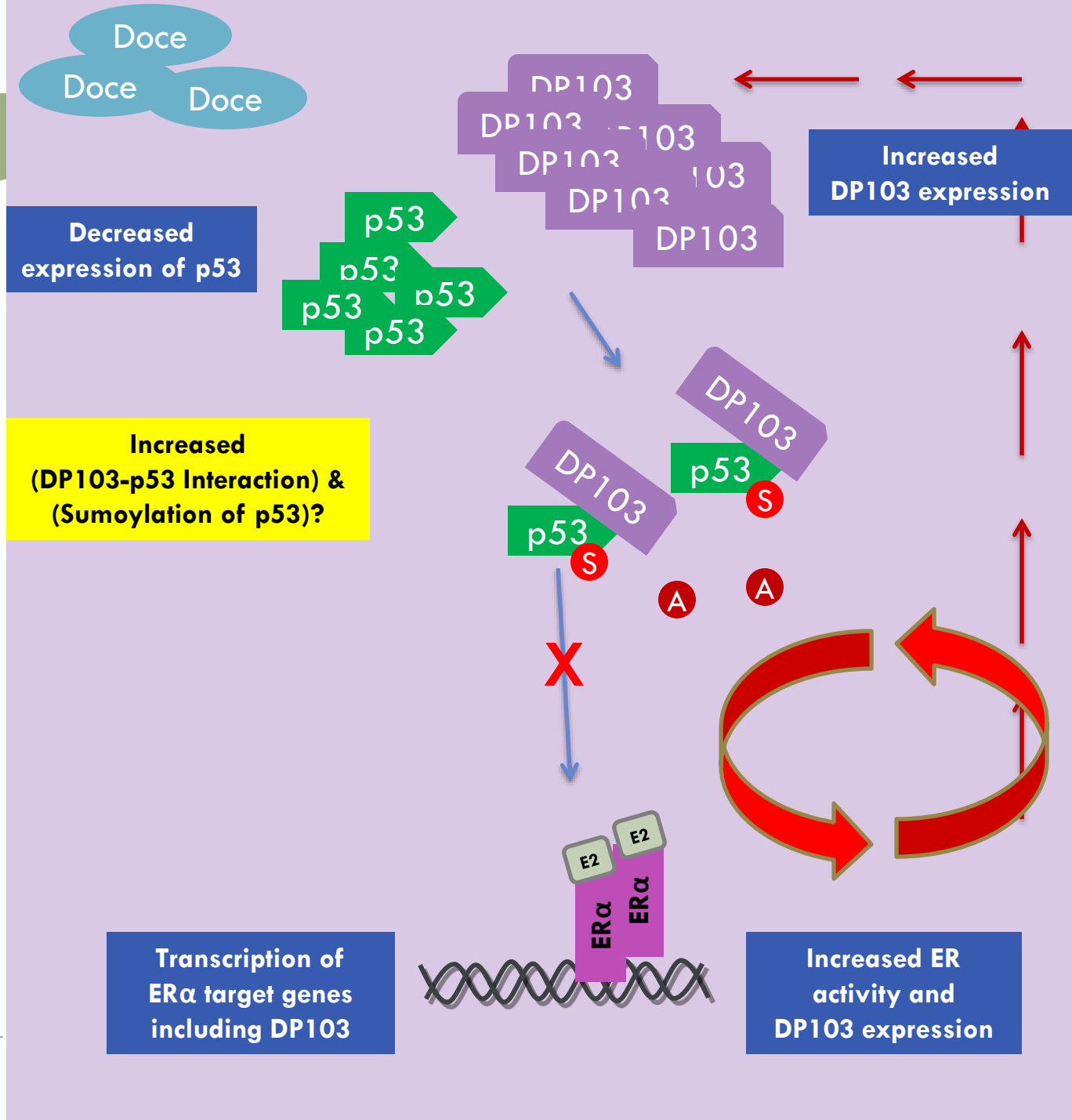
Responders



S Sumo group

A Acetyl group

Non-Responders



S Sumo group

A Acetyl group

Thank you!