



## Preliminary Data for MESI-STRAT

**ER activity regulates IDO1 induction via  
MAPK and mTOR signaling**

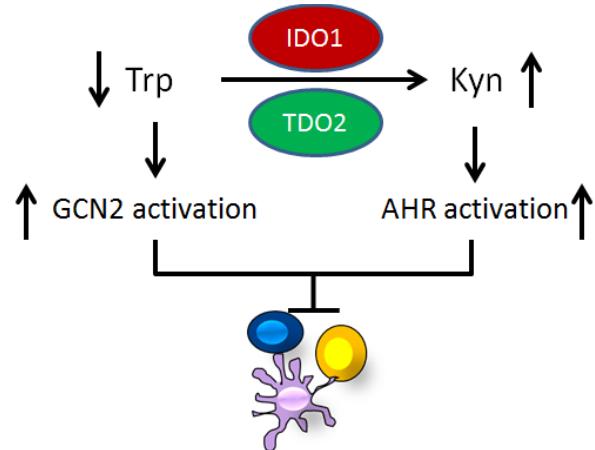
**Christiane Opitz**  
**MESI-STRAT Kickoff Meeting 29.03.2018**



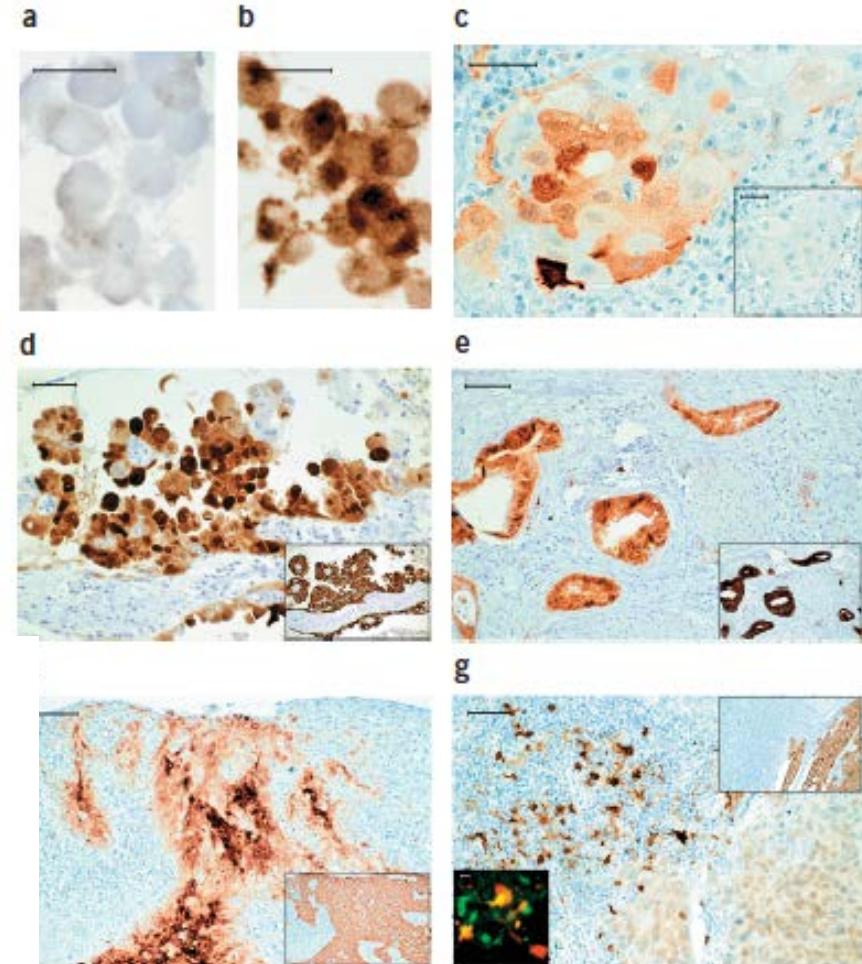
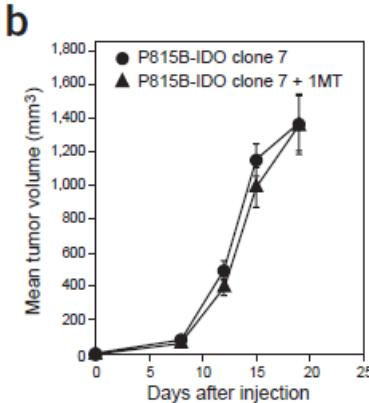
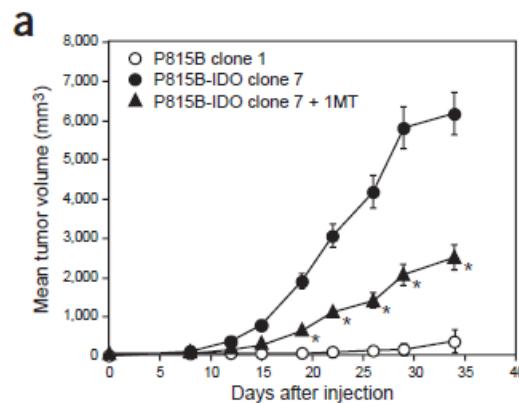
GERMAN  
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50 Years – Research for  
A Life Without Cancer

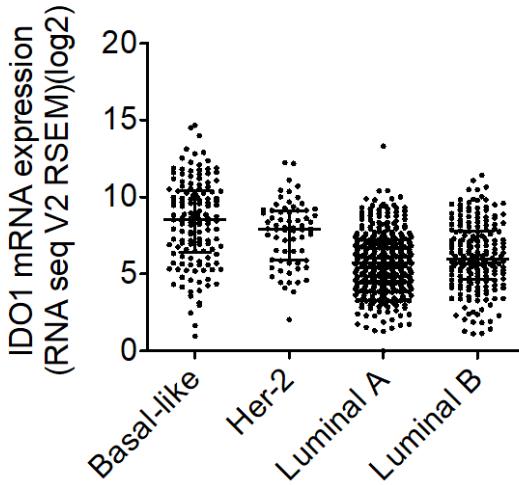
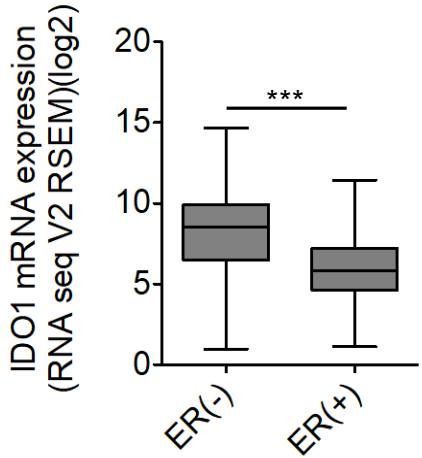
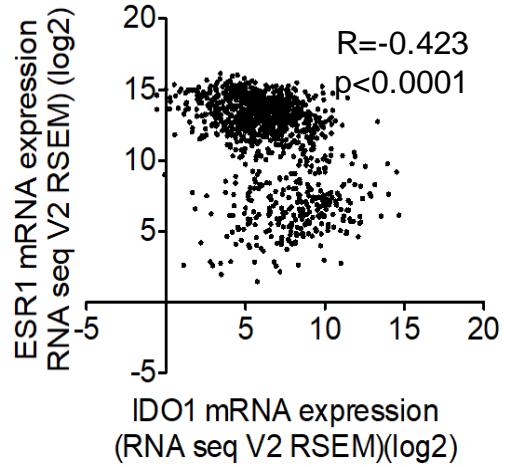
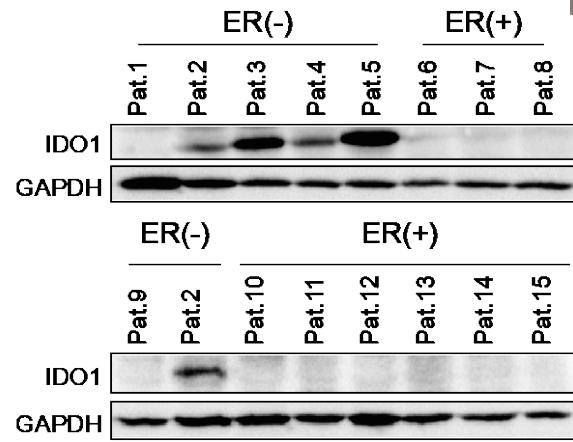
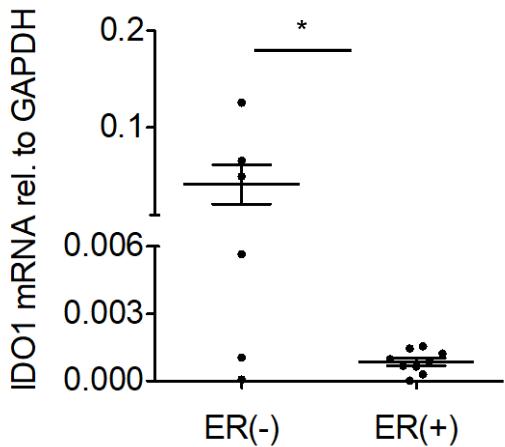
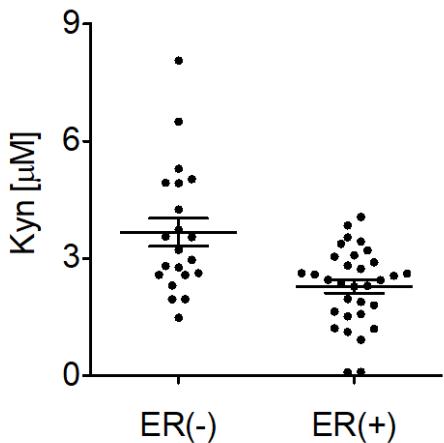
# IDO is expressed in tumors and inhibits anti-tumor immune responses



Suppression of effector T cell responses  
Differentiation of Tregs  
Increase in cancer cell motility

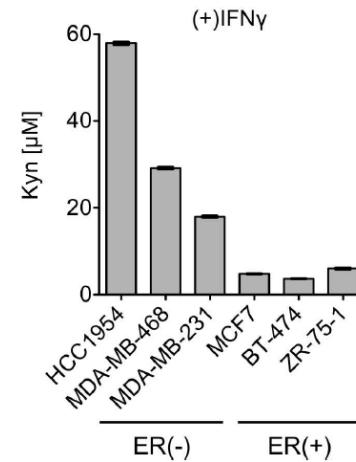
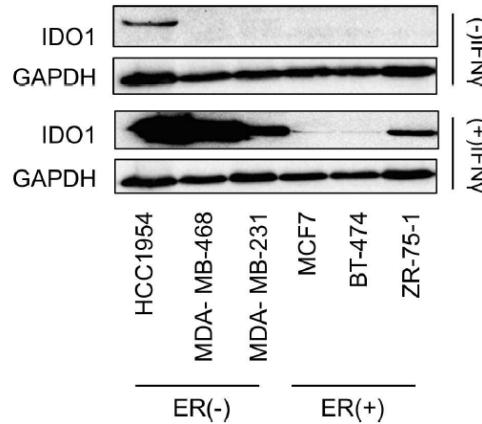
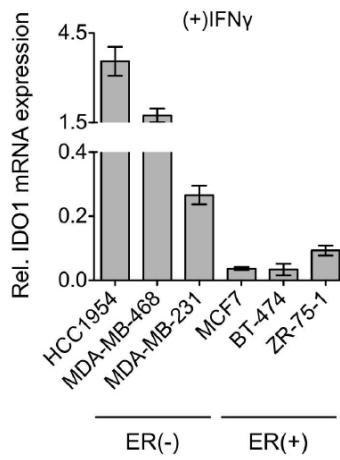
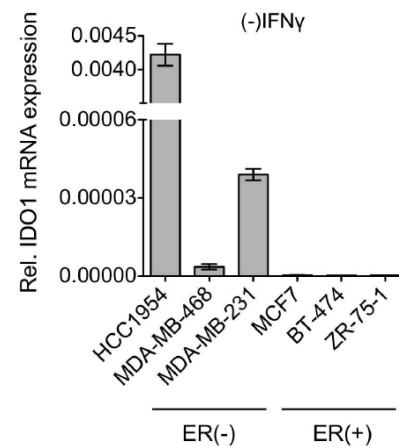
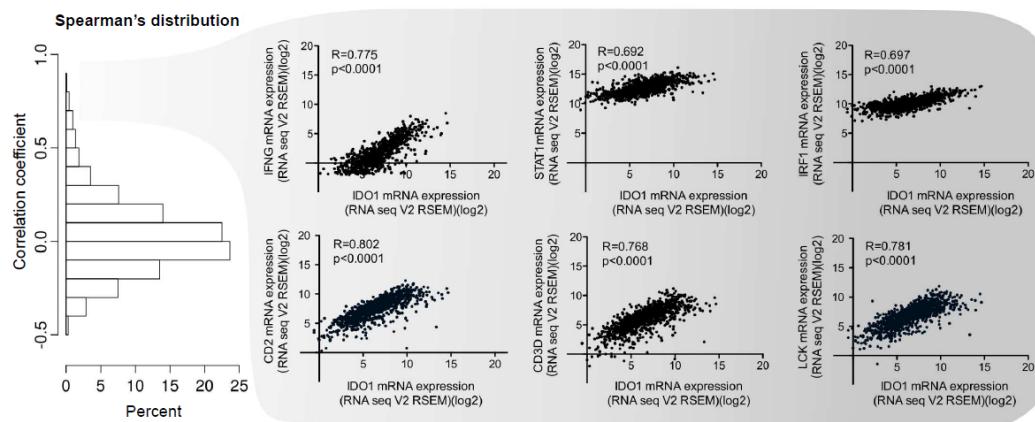


# Serum Kyn and tumoral IDO1 expression are lower in ER-positive than ER-negative breast cancer patients



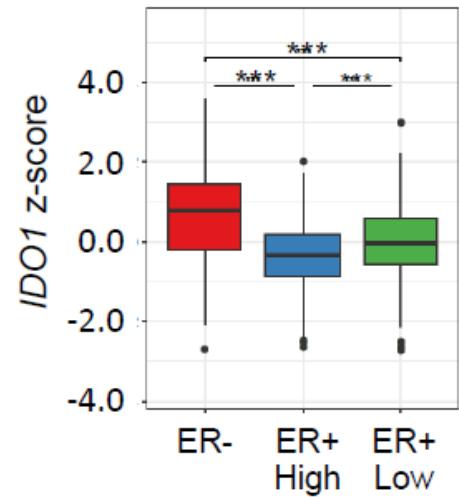
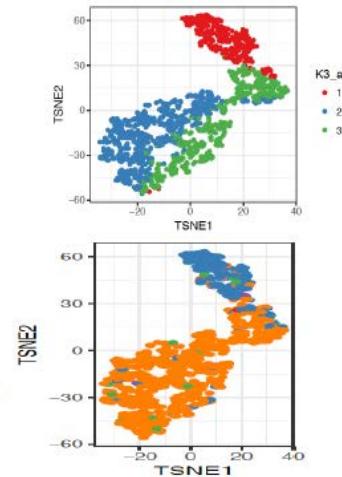
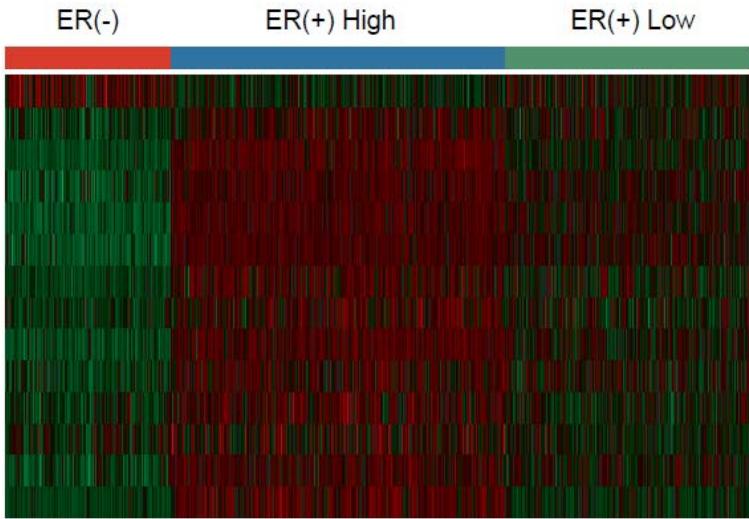
Dewi et al., 2017 Oncoimmunology

# IDO1 expression and activity is reduced in ER+ breast cancer cells



Dewi et al., 2017 Oncoimmunology

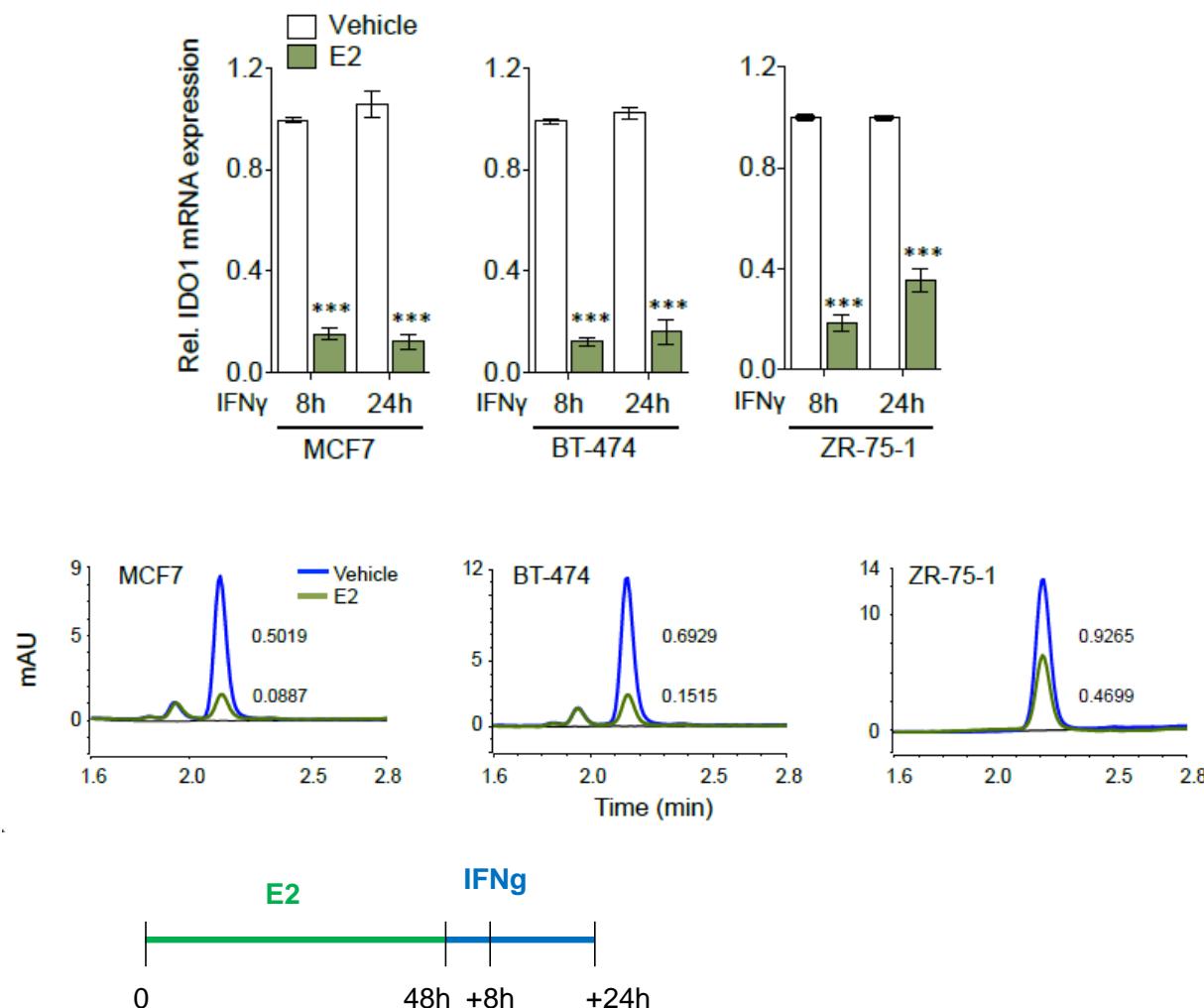
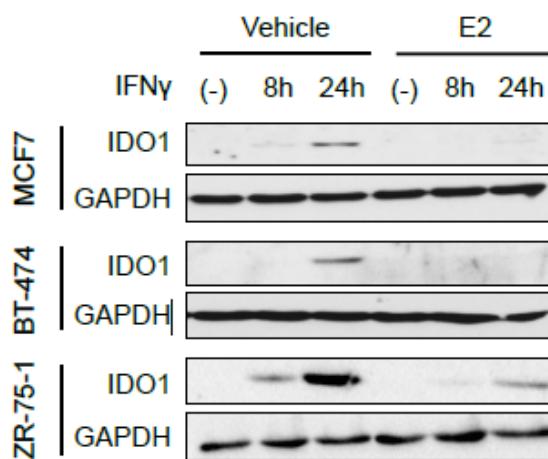
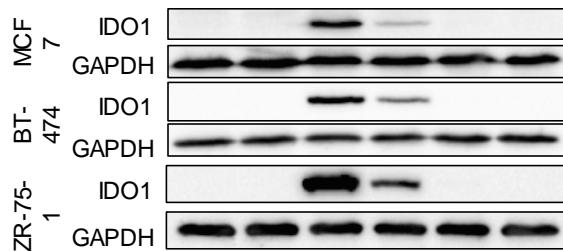
# ER activity suppresses IDO1 expression in human breast cancer tissue



Dewi et al., unpublished

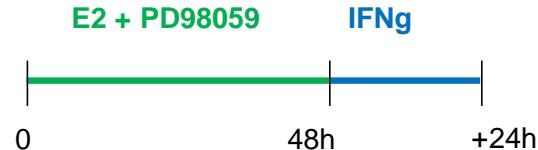
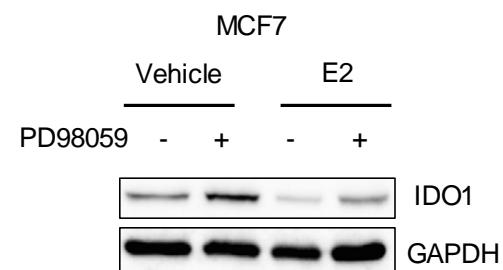
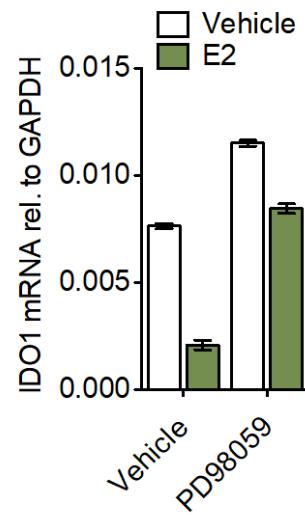
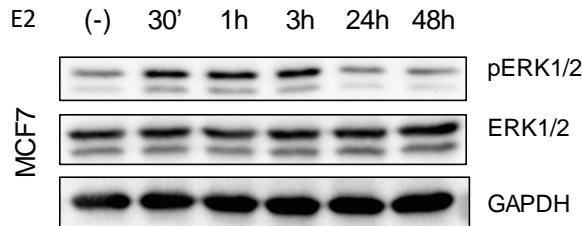
# Activation of ER signaling suppresses IDO1 induction in ER-positive breast cancer cells

T-cell supernatant	-	-	+	+	+	+	+
IFNg Ab	-	-	-	-	+	+	+
E2	-	+	-	+	-	-	+



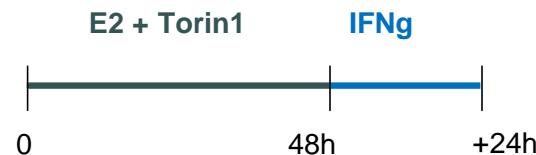
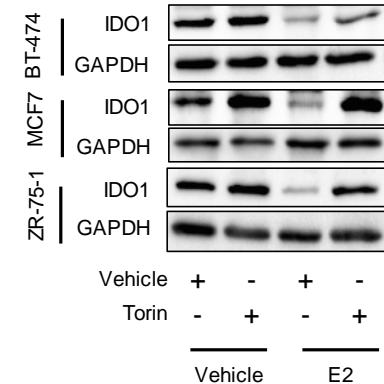
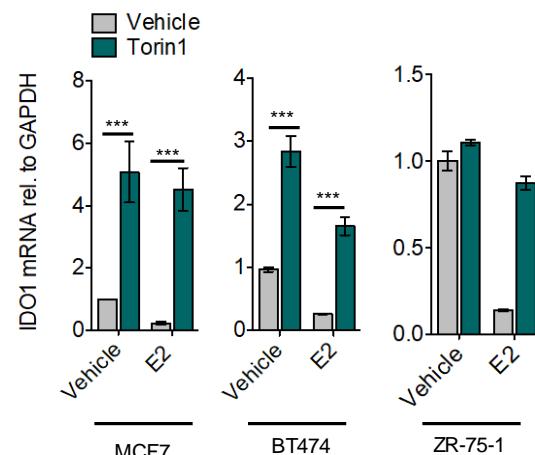
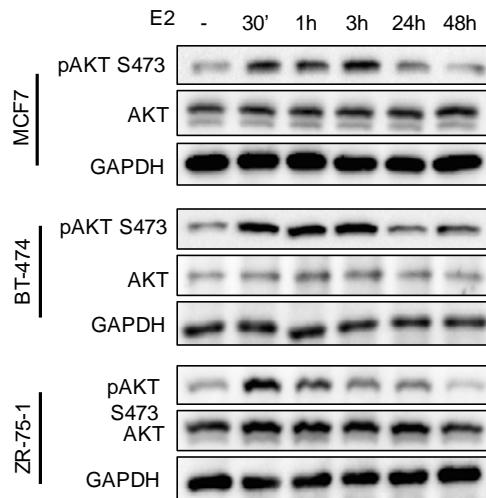
Dewi et al., unpublished

## Inhibition of Erk1/2 augments IDO1 induction and rescues ER-mediated IDO1 repression



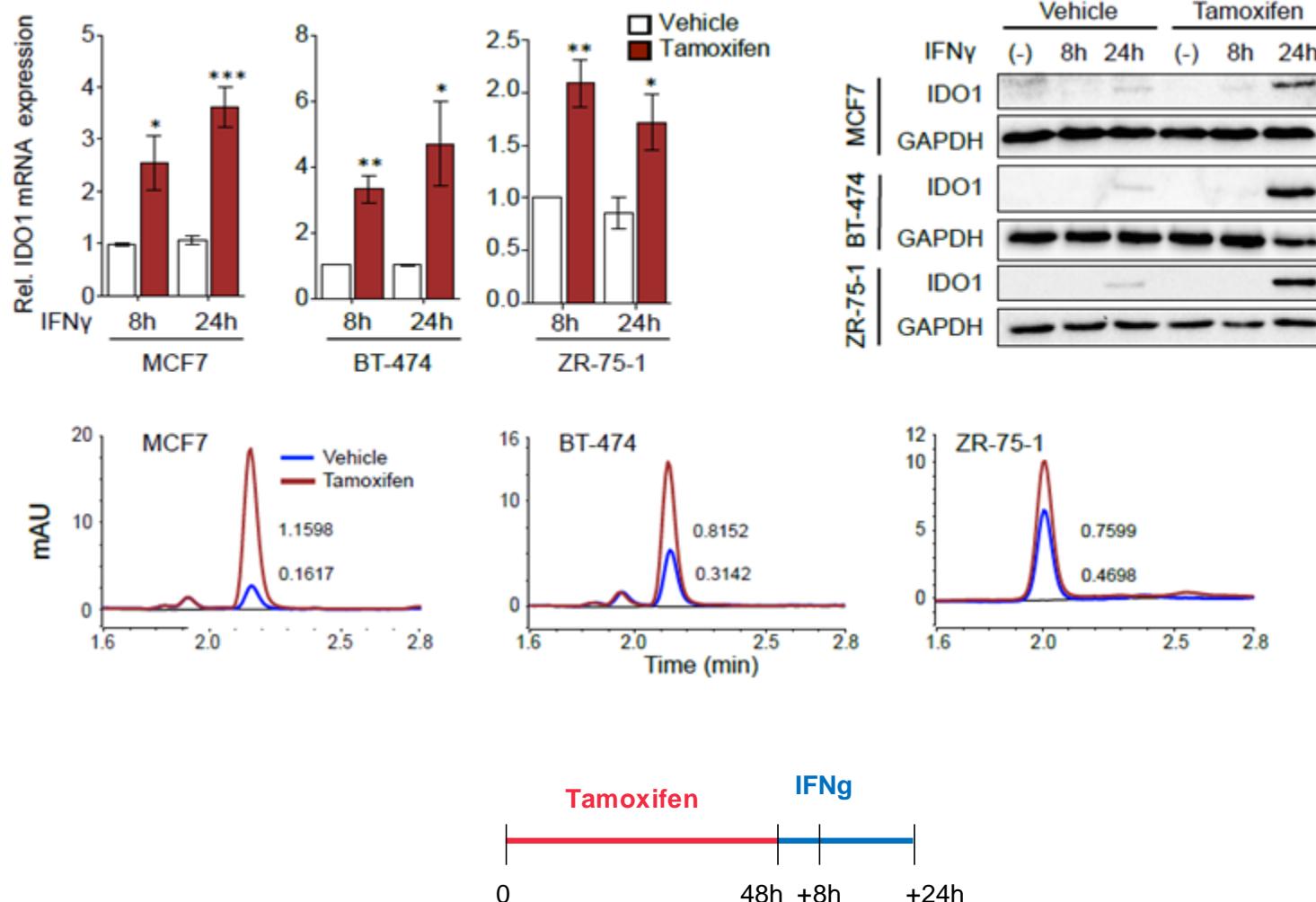
Dewi et al., unpublished

# Inhibition of mTOR enhances IDO1 induction and rescues ER-mediated IDO1 repression



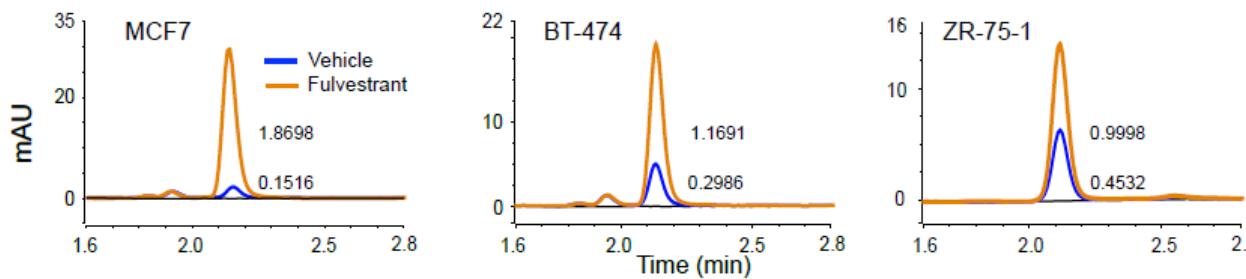
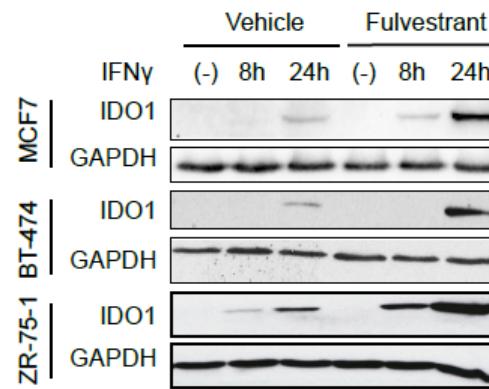
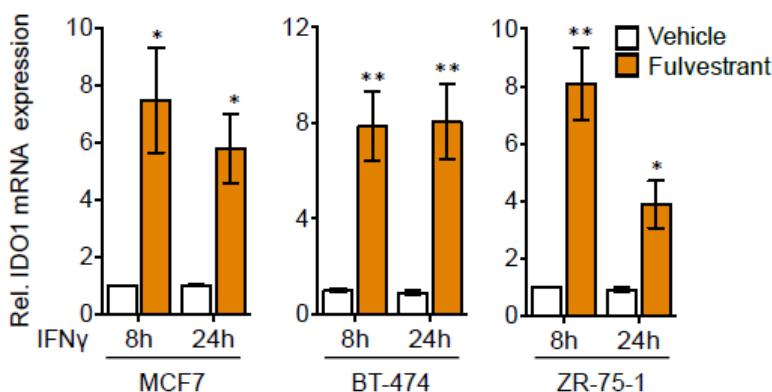
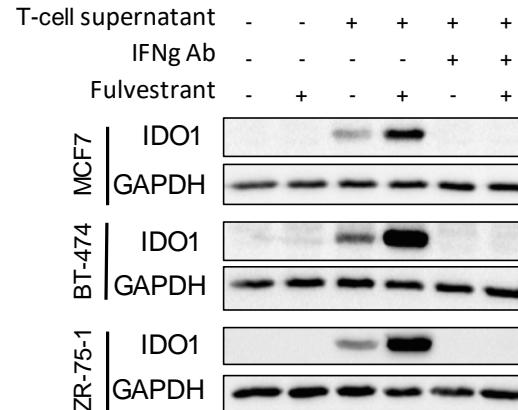
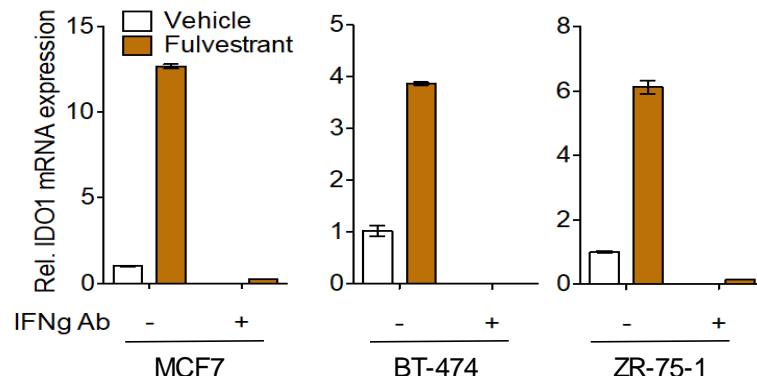
Dewi et al., unpublished

# Pharmacological inhibition of ER by Tamoxifen augments IDO1 induction



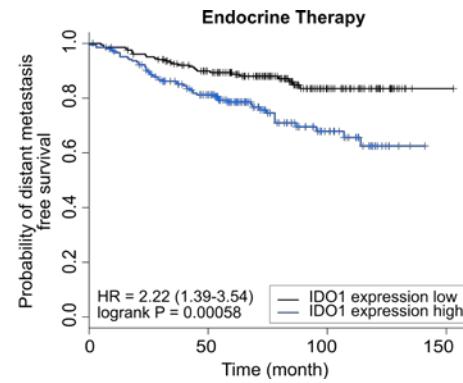
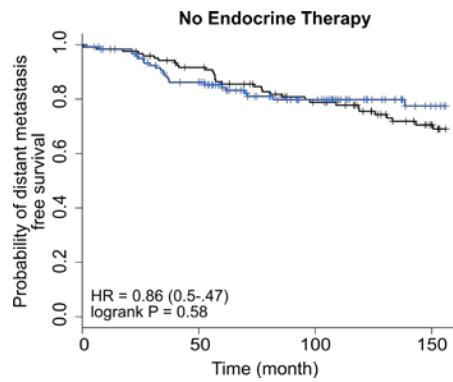
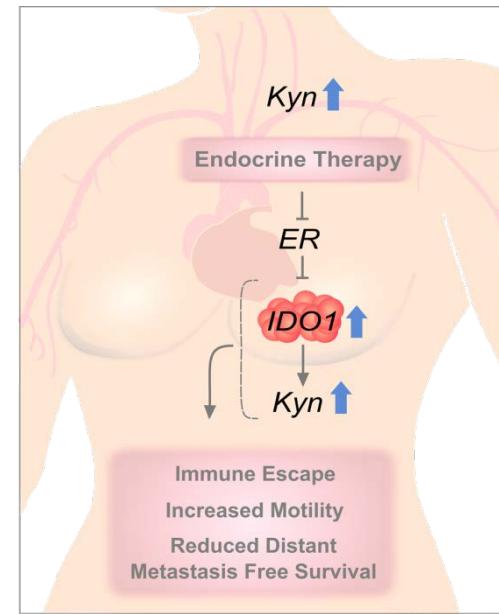
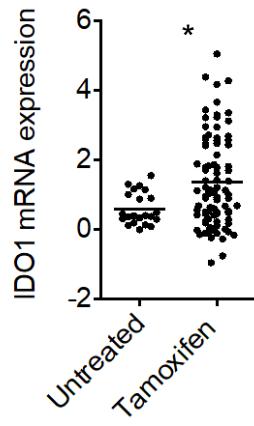
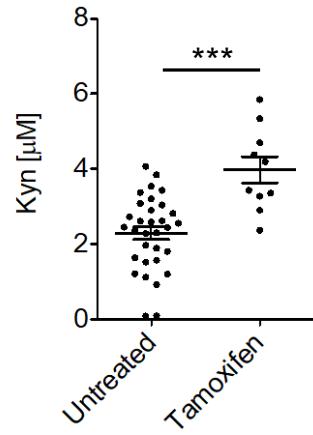
Dewi et al., unpublished

# Pharmacological inhibition of ER by Fulvestrant augments IDO1 induction



Dewi et al., unpublished

# IDO1 expression and activity are upregulated through endocrine therapy and affect breast cancer cell motility as well as distant metastasis free survival



Dewi et al., unpublished

UFZ, Leipzig  
Saskia Trump

Gynecology, Dresden  
Jan-Dominik Kuhlmann  
Pauline Wimberger

Gynecology, Heidelberg  
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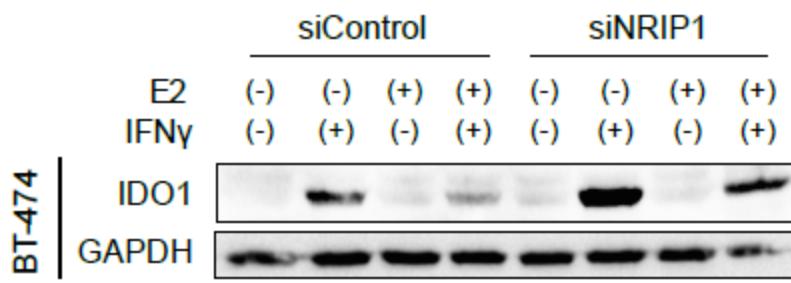
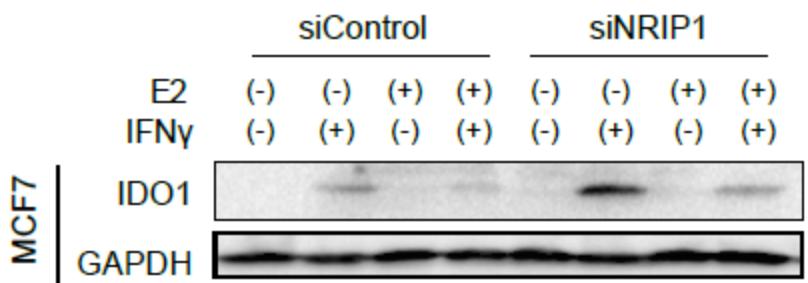
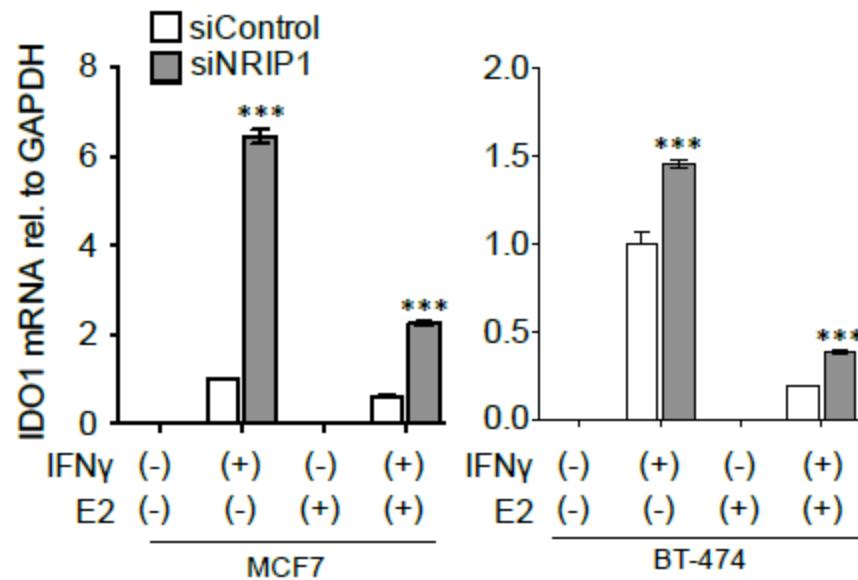
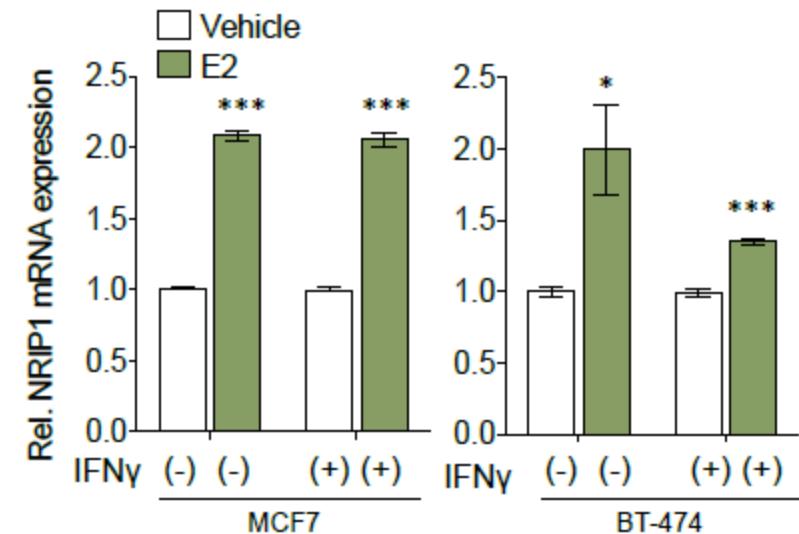


**dkfz.**

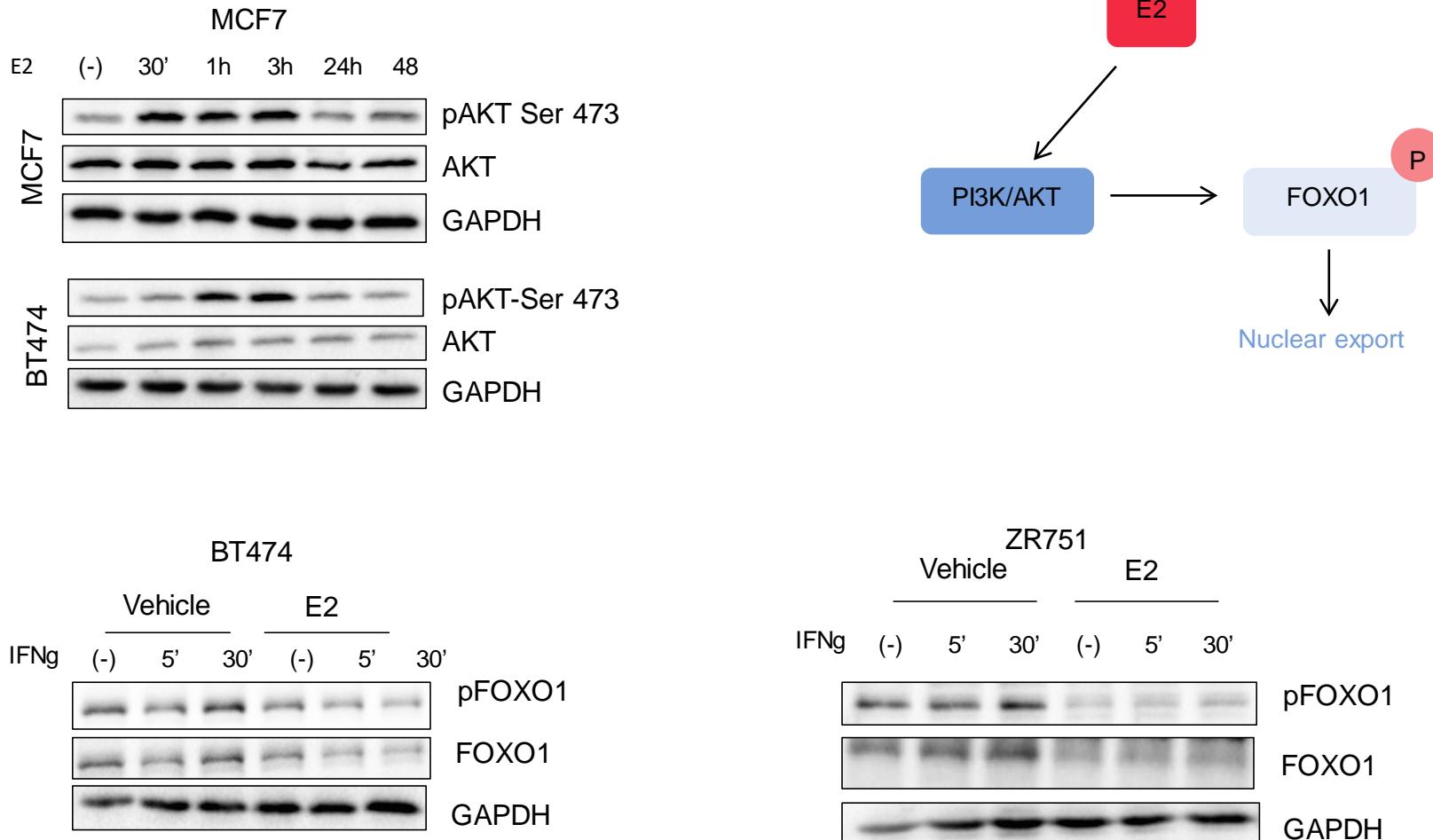
GERMAN  
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50 Years – Research for  
A Life Without Cancer

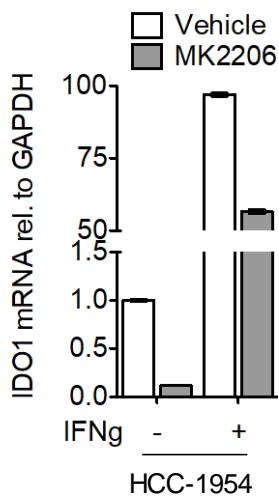
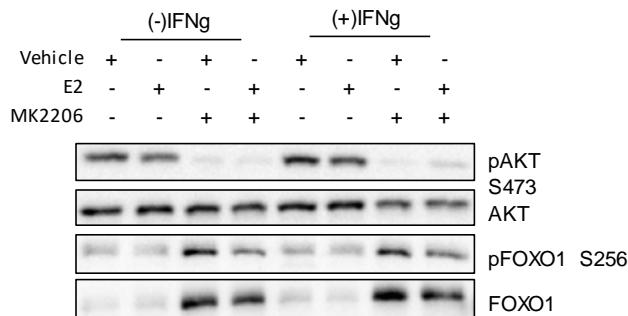
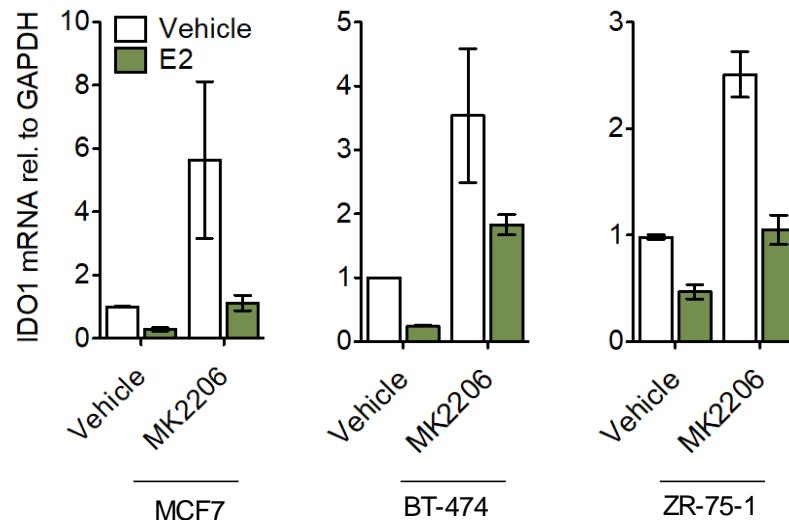
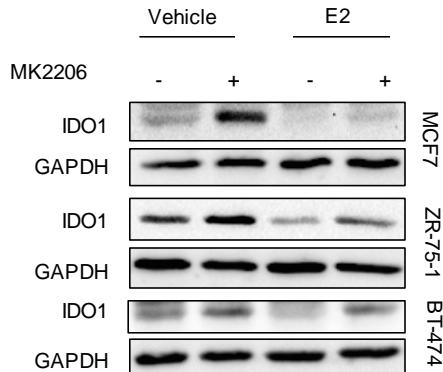
# ER activation suppresses IDO1 expression via the ER corepressor NRIP1



## E2 stimulates PI3K/AKT signaling



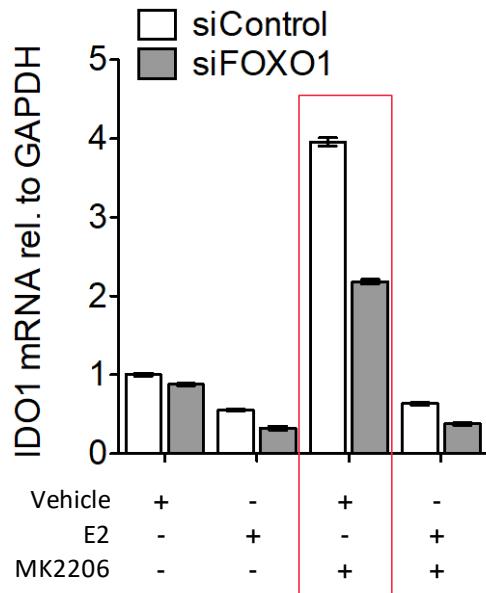
# Inhibition of Akt augments IDO1 induction and rescues the ER mediated IDO1 repression



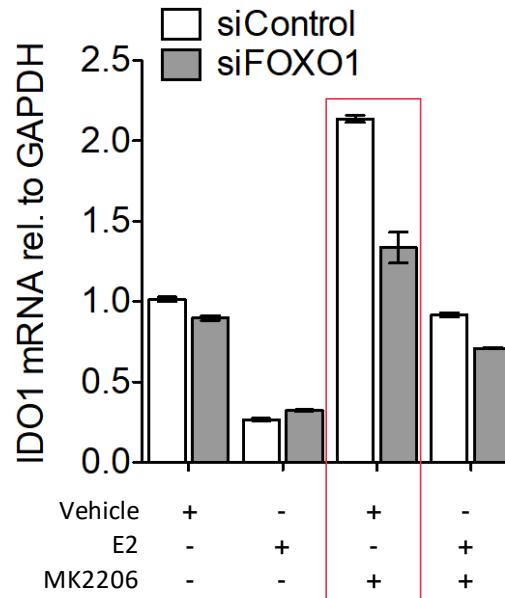
Akt inhibition reduces IDO1 in ER(-) IDO1 constitutively expressing cells

## Induction of IDO1 by Akt inhibitor is repressed by FOXO1 knockdown

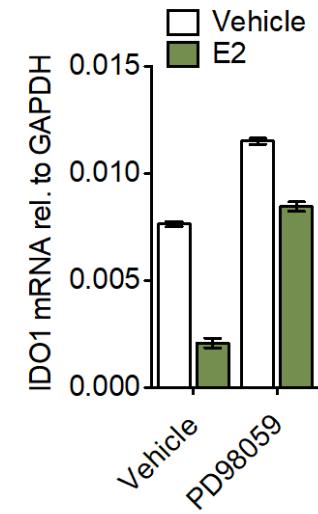
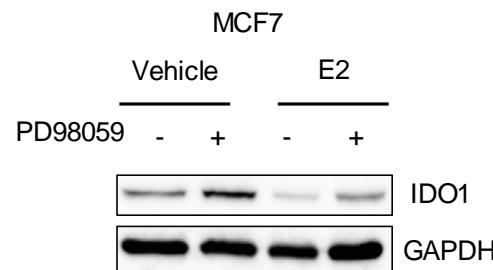
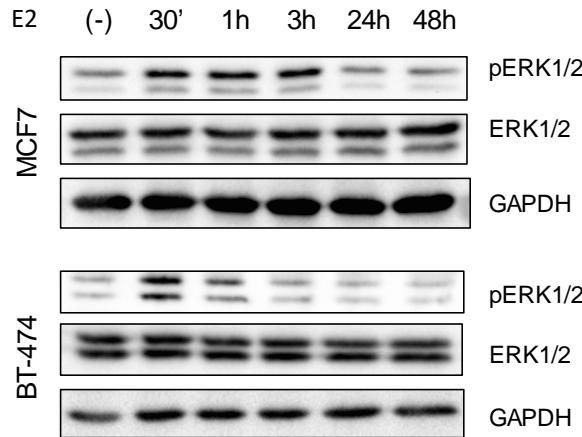
MCF7



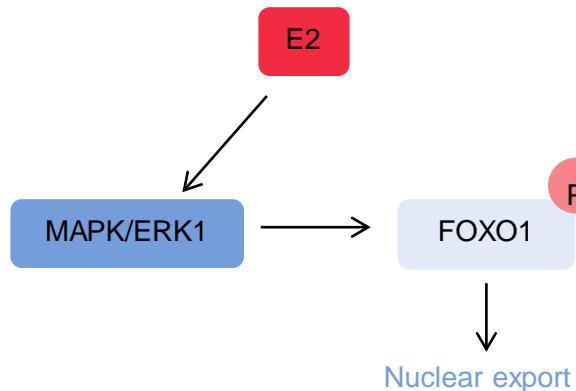
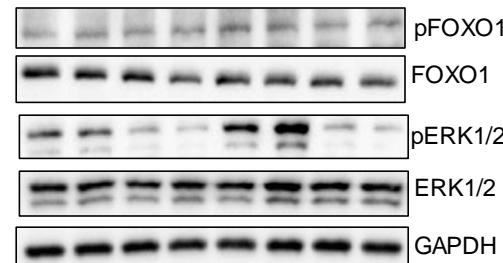
ZR-75-1



# Inhibition of Erk1/2 augments IDO1 induction and rescues the ER mediated IDO1 repression



Vehicle	+	-	+	-	+	-	+	-
E2	-	+	-	+	-	+	-	+
PD98059	-	-	+	+	-	-	+	+
IFNg	-	-	-	-	+	+	+	+

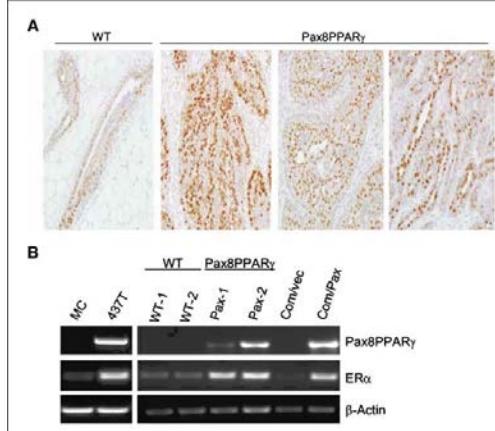


# In vivo model of ER(+) breast cancer

## Research Article

### Inhibition of Peroxisome Proliferator-Activated Receptor $\gamma$ Increases Estrogen Receptor-Dependent Tumor Specification

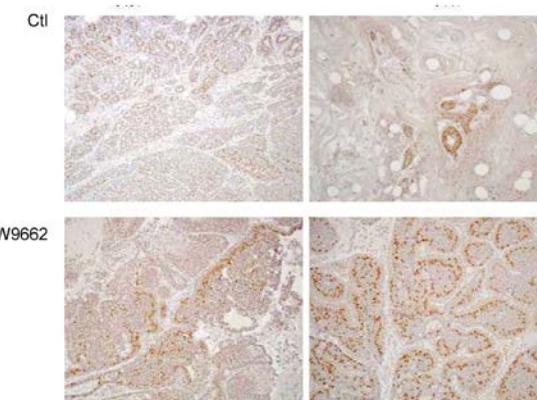
Yuzhi Yin,<sup>1</sup> Hongyan Yuan,<sup>1</sup> Xiao Zeng,<sup>1</sup> Levy Kopelovich,<sup>2</sup> and Robert I. Glazer<sup>1</sup>



(Cancer Res. 69:687-94, 2009)

### Drug-Targeted Inhibition of Peroxisome Proliferator-Activated Receptor Enhances the Chemopreventive Effect of Anti-Estrogen

Hongyan Yuan<sup>1</sup>, Levy Kopelovich<sup>2</sup>, Yuzhi Yin<sup>1,3</sup>, Jin Lu<sup>1</sup> and Robert I. Glazer<sup>1</sup>



Gene symbol	Gene Title	Fold Change	WT	GW9662
Ido1	indoleamine 2, 3-dioxygenase 1	-4.8	406	85

(Oncotarget. 3:345-56, 2012)

## Outlook

- Addressing the role of PI3K-AKT-FOXO1 axis in mediating IDO1 repression by ER.
- Studying T cell proliferation in conditioned medium from ER-positive breast cancer cell lines treated with endocrine therapy.
- Studying IDO1 induction under endocrine therapy after T cell supernatant treatment in a tumor explant model, maintained in a perfusion-based Bioreactor (in collaboration).