The impact of chemotherapy on TMEM-mediated cancer cell dissemination

Maja H. Oktay, MD/PhD
Professor of Pathology
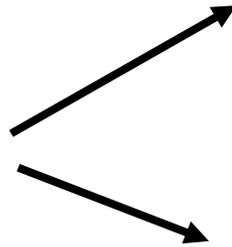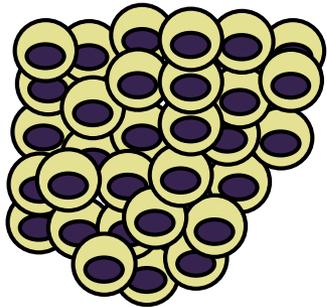*Professor of Anatomy and Structural Biology*
Albert Einstein College of Medicine/ Montefiore Medical Center, New York

Increased use of <u>pre-operative (neoadjuvant) chemotherapy</u> in breast cancer patients
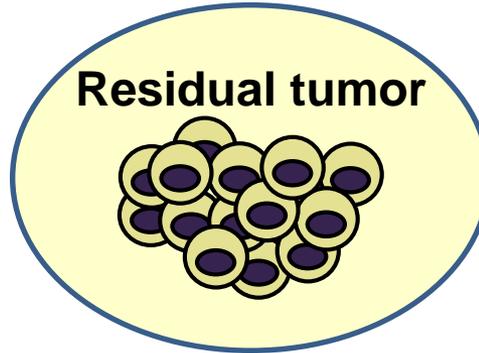
1. Chemotherapy

2. Surgery

Primary tumor

No tumor → **Excellent long term prognosis**
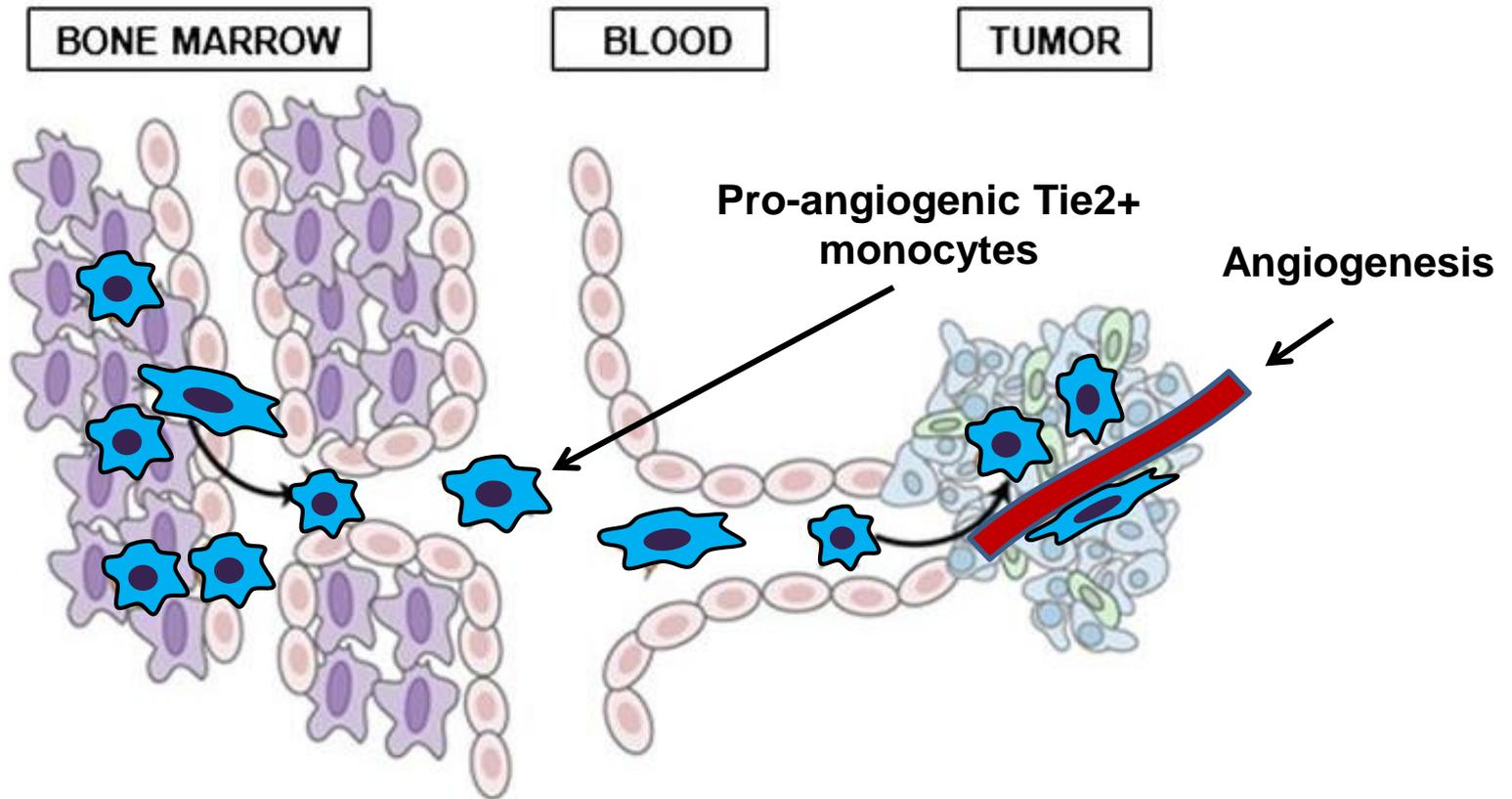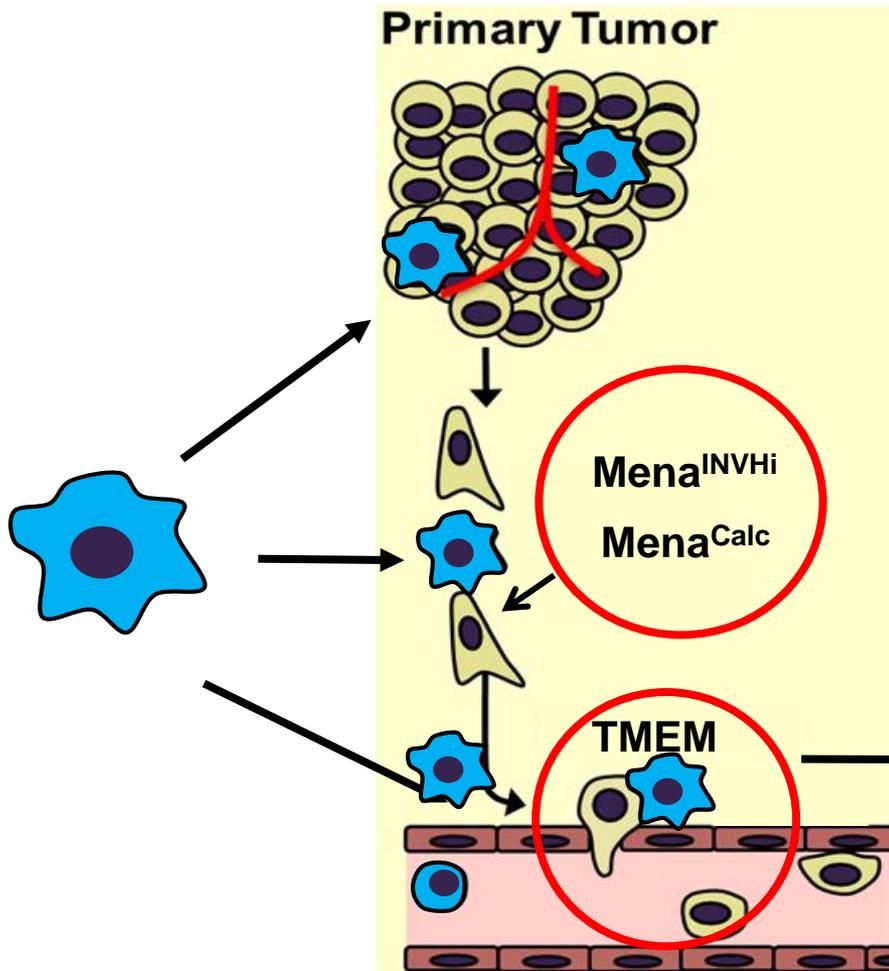
Residual tumor → **Uncertain long term prognosis**

Chemotherapy Induces Cell Death & Hypoxia

➡ **Tissue Repair**

BONE MARROW   BLOOD   TUMOR

Pro-angiogenic Tie2+ monocytes

**Angiogenesis**

Roodhart et al. Blood 2013
Hughes et al Cancer Res 2015
*Chen et al Cancer Res 2016*

Pro-metastatic Tumor Microenvironment

1. Does chemotherapy affect the density and activity of TMEM sites?

2. Does chemotherapy affect the expression of Mena isoforms?

TMEM = Doorway for cancer cell dissemination!

Pignatelli et al, Sci. Reports, 2016

Harney at al, Cancer Disc, 2015

1. Chemotherapy Increases TMEM Score in <u>Breast Cancer Patients with Residual Tumor After Neoadjuvant Chemotherapy</u>

Rohan et al. JNCI, 2014
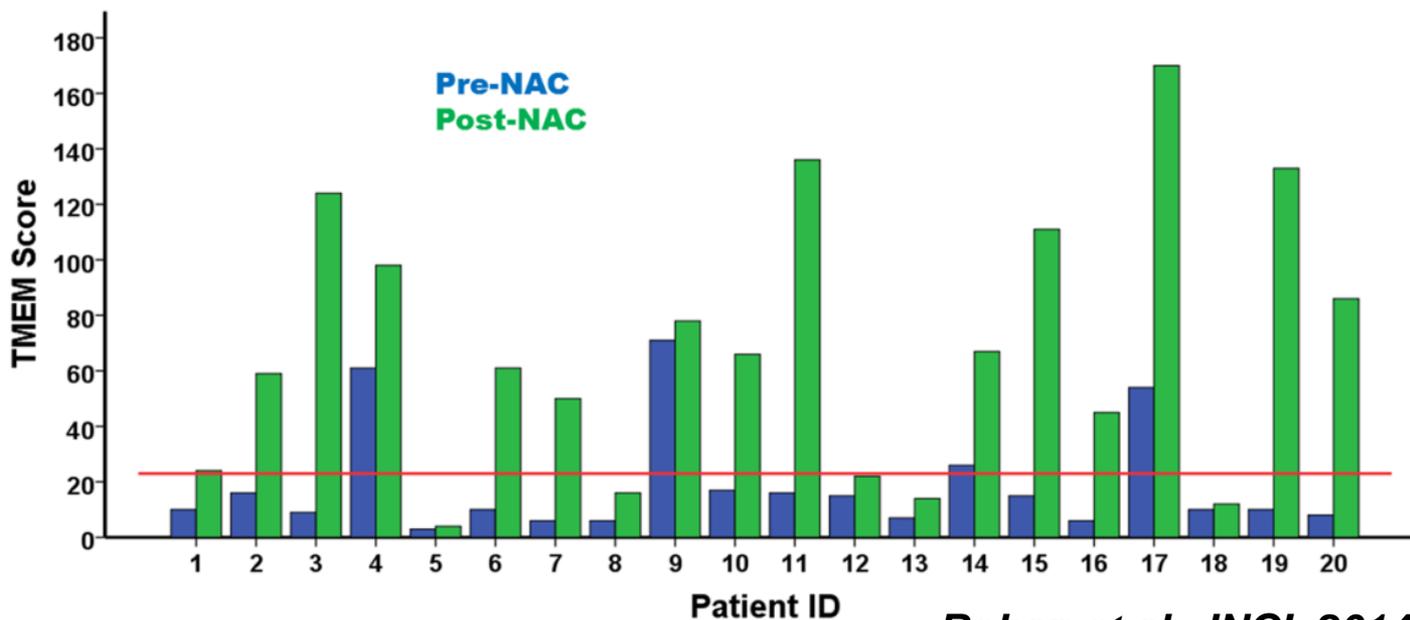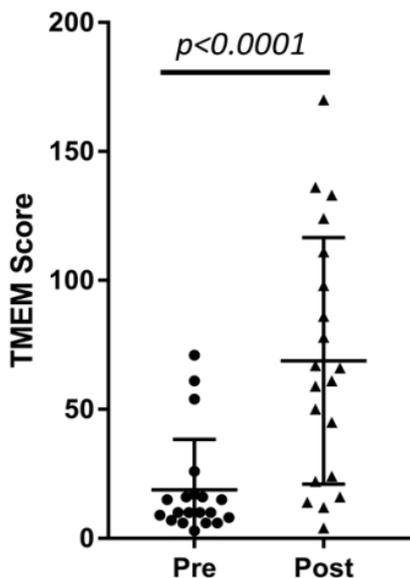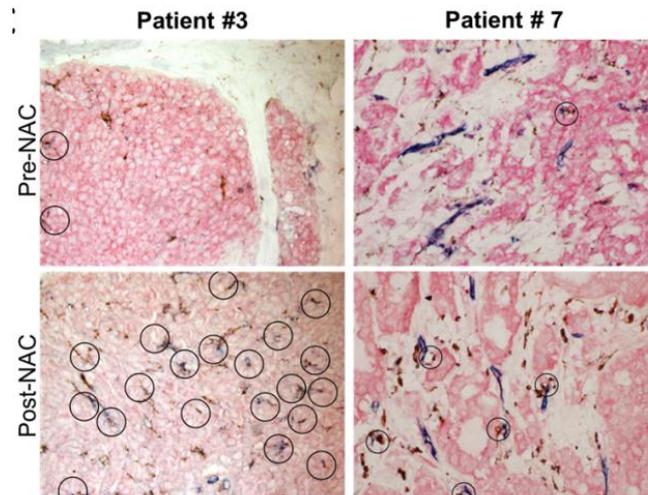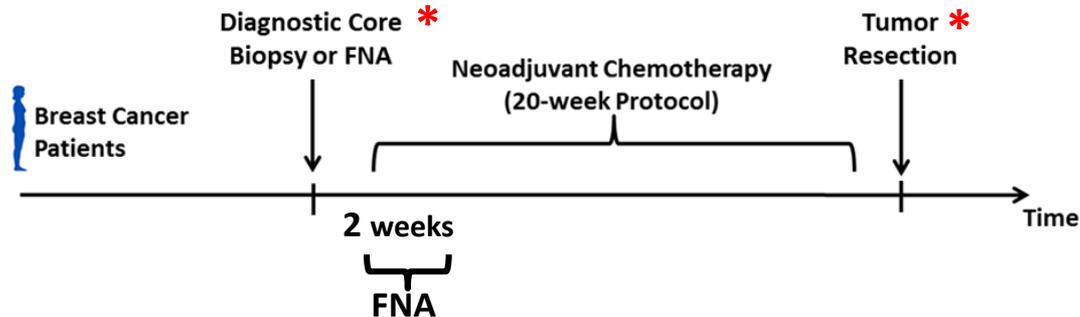
2. Chemotherapy Increases Mena^{INV} Expression in <u>Breast Cancer Patients with Residual Tumor After Neoadjuvant Chemotherapy</u>
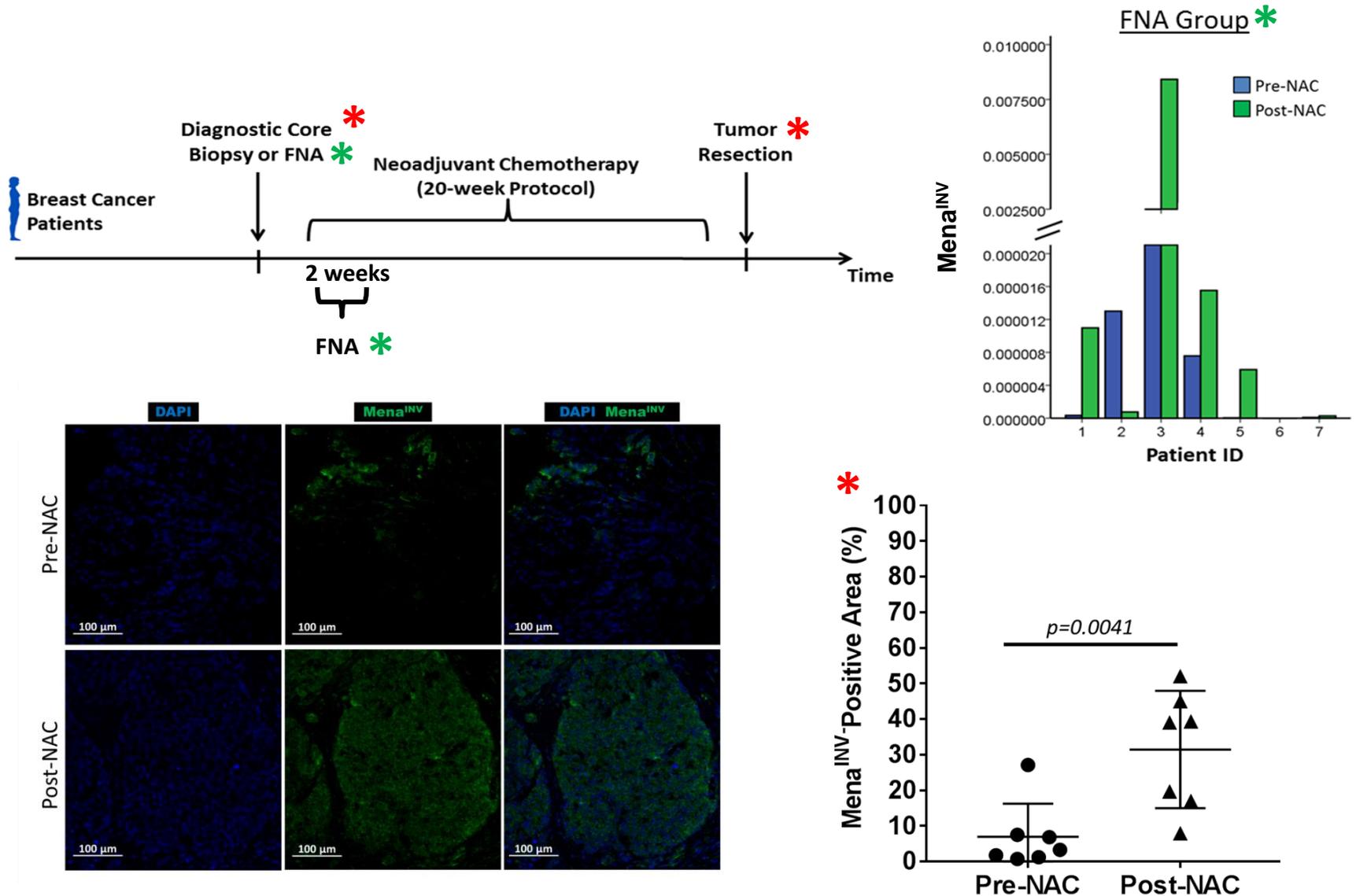
# TMEM and Mena^{Calc} are Prognostic Markers of Outcome in Breast Cancer

TMEM

Robinson et al 2009 Clinical Can. Res.	30 case-control pairs (60 cases)
Rohan et al 2014 JNCI	259 case-control pairs (518) cases)
Sparano et al in press, npj Breast Cancer	660 cases

Mena^{Calc} (panMena-Mena11a = all invasive Isoforms of Mena)

Agarwal et al 2012 Breast Cancer Res.	797 cases
Forse et al 2015 BMC Cancer	406 cases

These markers predict distant recurrence ([dissemination](#)) but not tumor growth as measured by **IHC-4** and **Oncotype Dx**.

# Study Design in Mouse Models
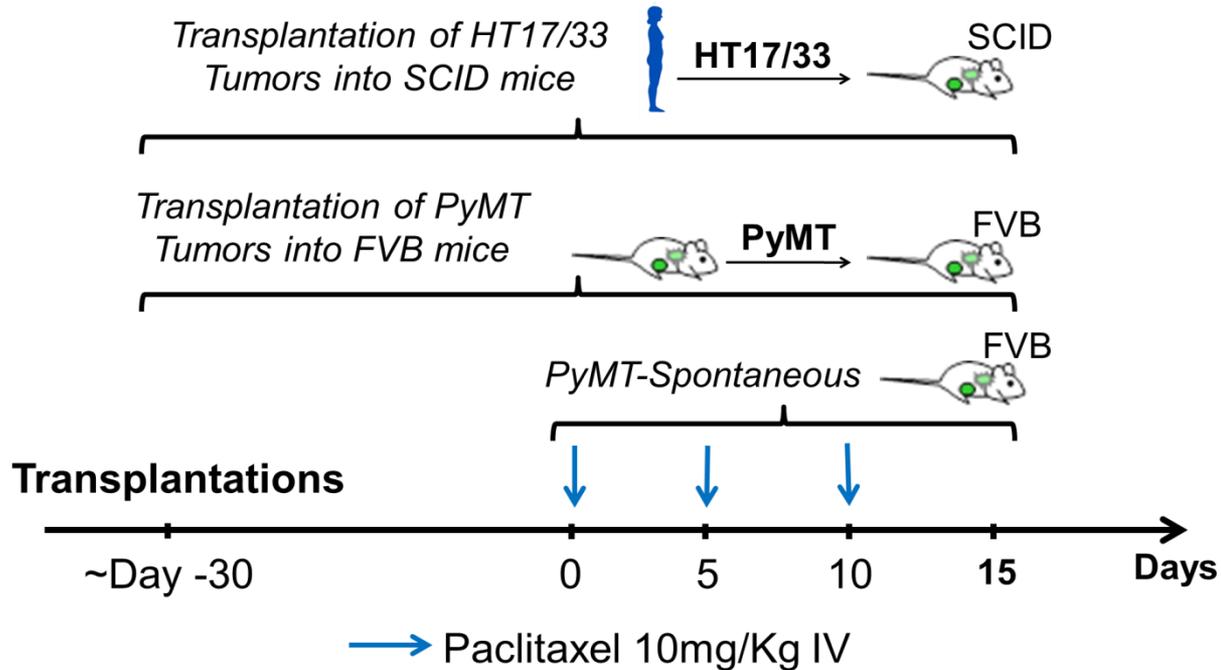
George Kargiannis, DVM, PhD

TMEM assembly

TMEM function
- **CTCs and**
- **Cancer cell dissemination to the lungs**

Mice *	ER Status	Control	Paclitaxel
PyMT-Spontaneous	+	N=11	N=10
PyMT-Transplantation	-	N=17	N=19
HT17-Xenograft	-	N=14	N=15
HT33-Xenograft	+	N=12	N=14

* N of mice corresponds to total number of mice included in the study. When assessing individual variables, the N may vary depending on the exclusion criteria.
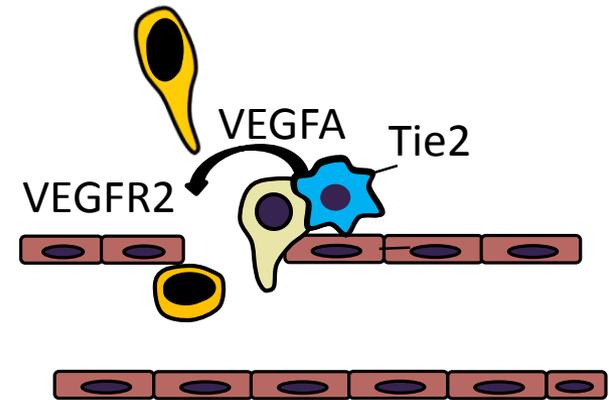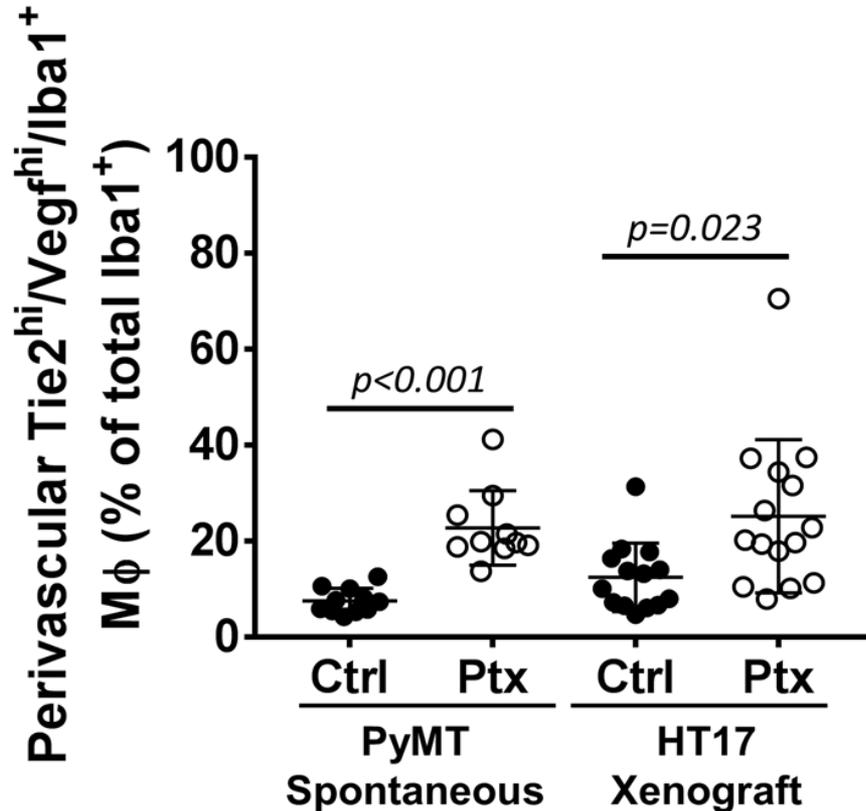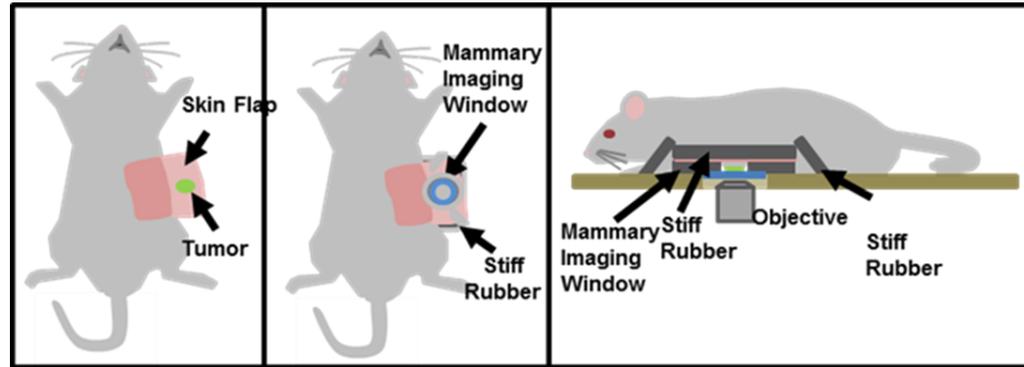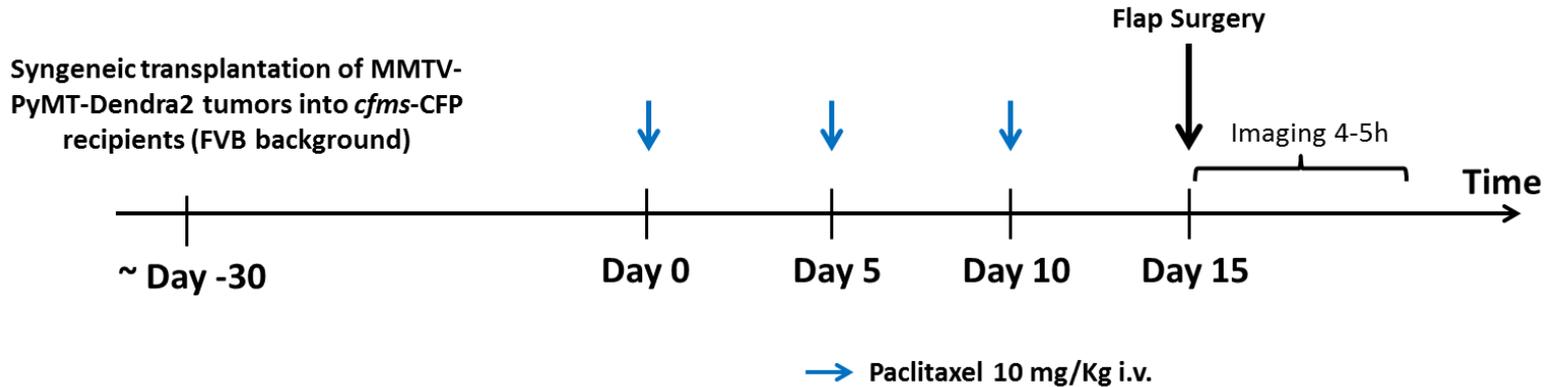
Paclitaxel Promotes TMEM Assembly
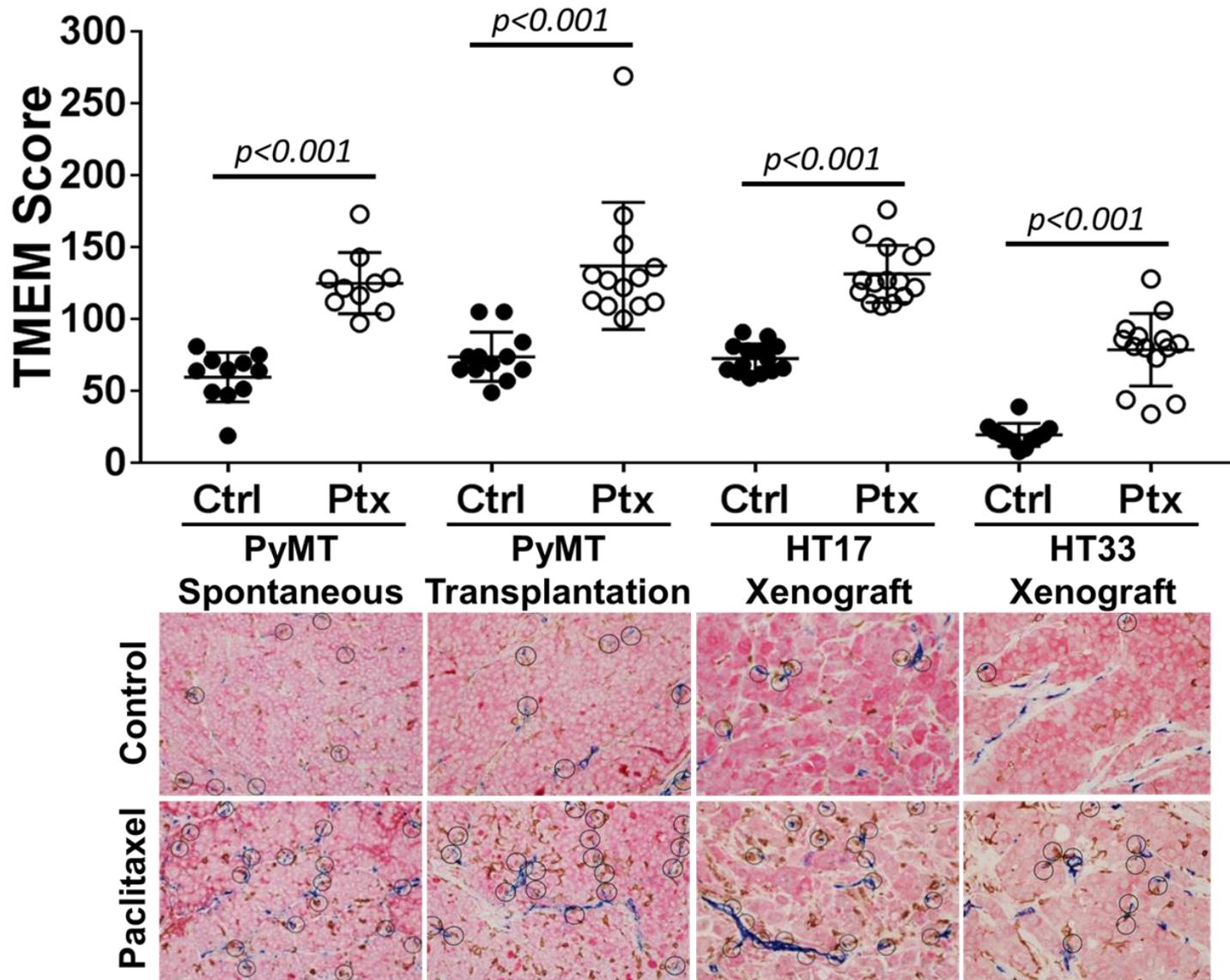
Paclitaxel Induces Influx of Tie2^{High}/ VEGF^{High} Macrophages

Are Paclitaxel Induced TMEM Sites Active?

Does Paclitaxel Increase the Incidence of Active TMEM (Transient Vascular Permeability or Bursting)?

David Entenberg, M.Sc
Senior Associate of ASB
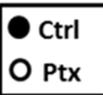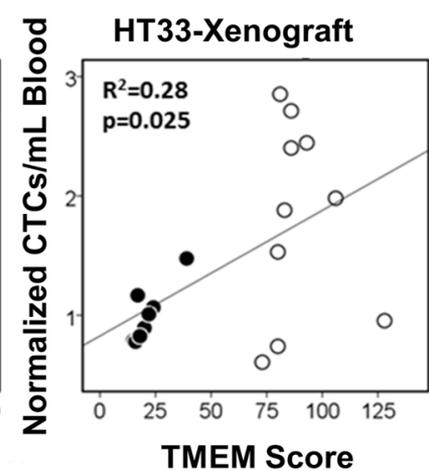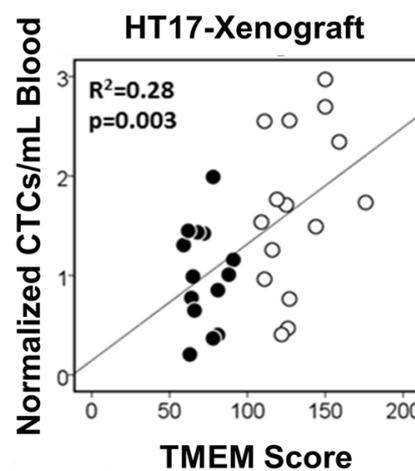**Director of Technology Development**
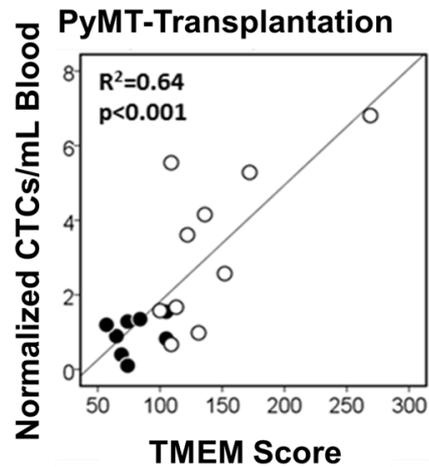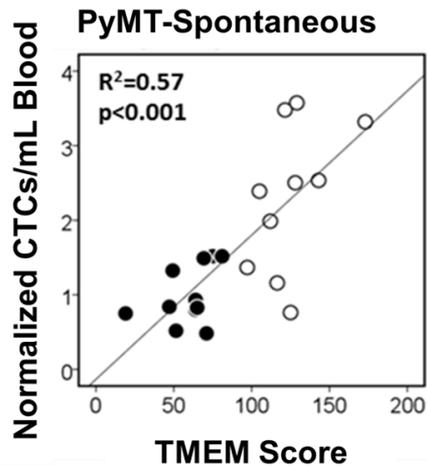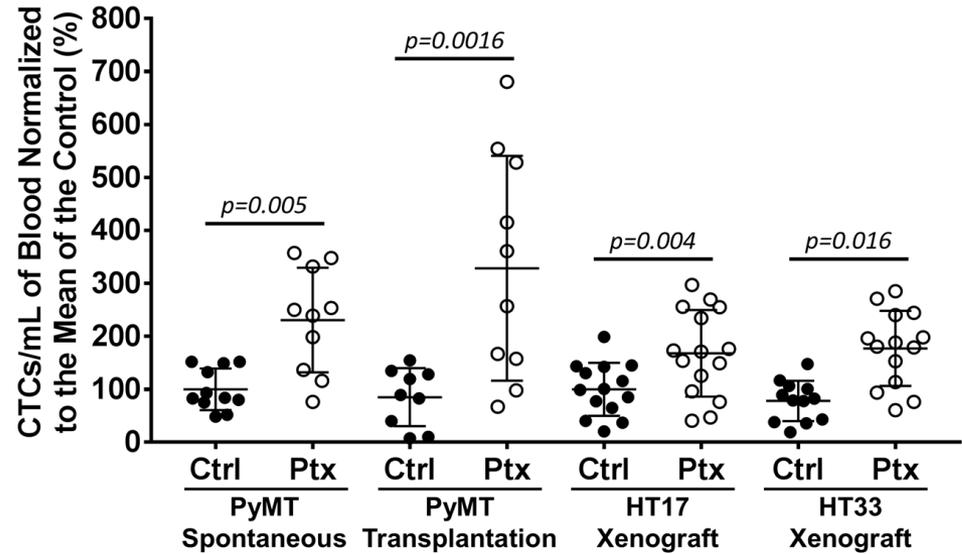**Director of Integrated Imaging**

Jessica Patoriza, MD
Surgery Resident, PGY-3
T32 Training Award Recipient
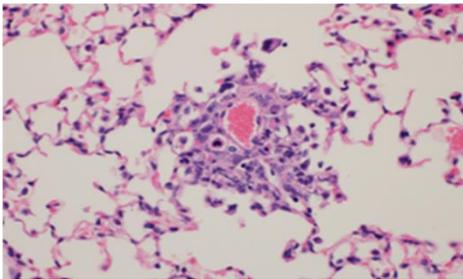
Paclitaxel Promotes TMEM Function (Bursting & CTCs)

Paclitaxel Promotes TMEM Function
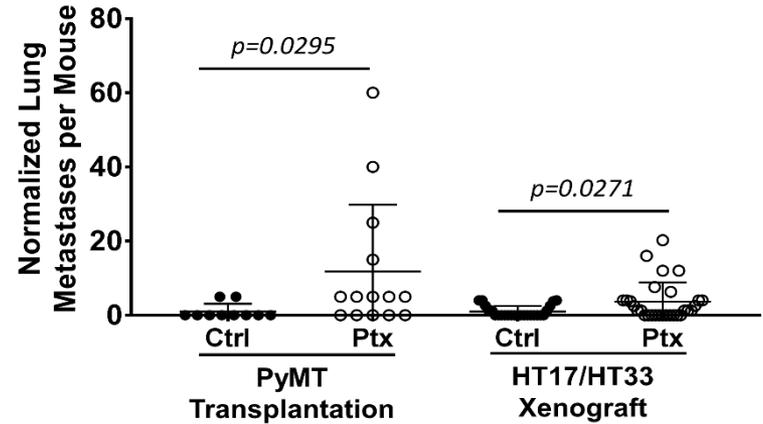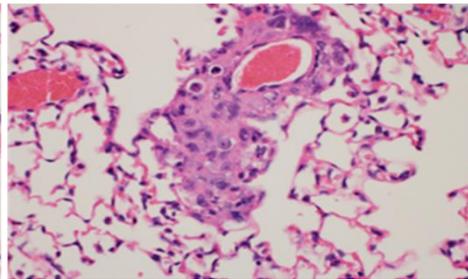# (Cancer Cell Dissemination to the Lungs)

Can Anti-metastatic Strategy be Designed to Counteract the Effect of Chemotherapy on TMEM Function?
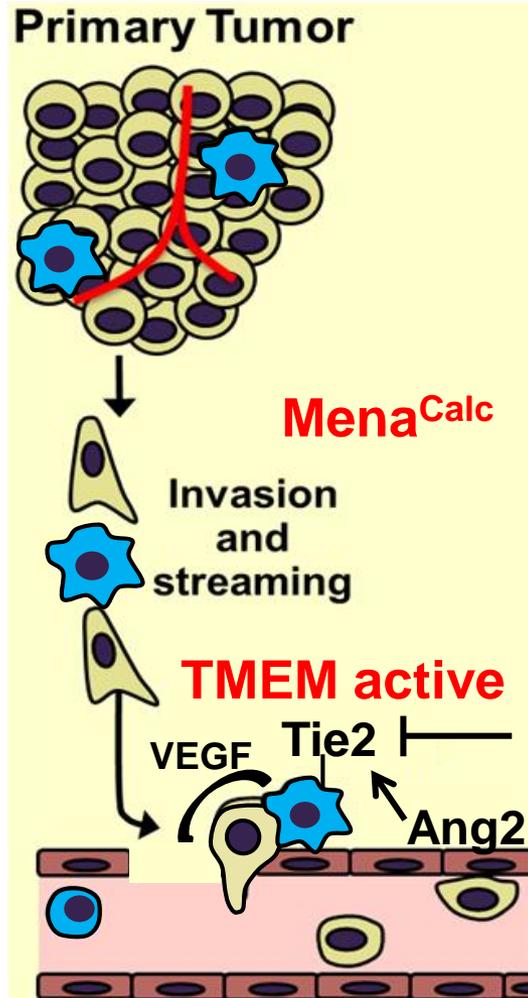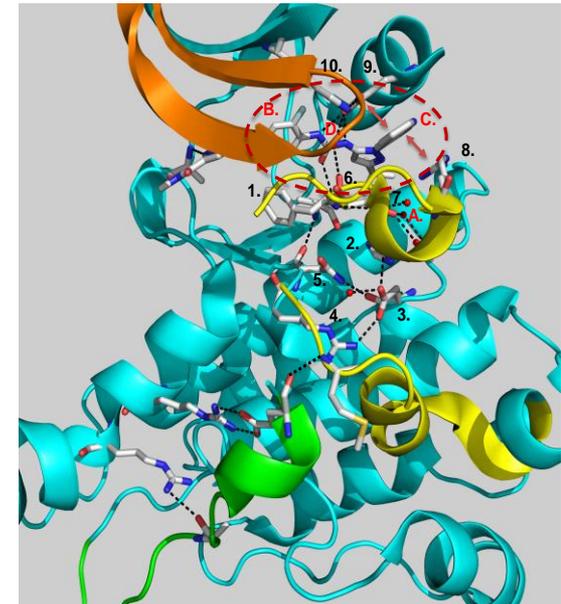
Switch pocket inhibitor

Rebastinib Blocks Paclitaxel-induced TMEM Activity
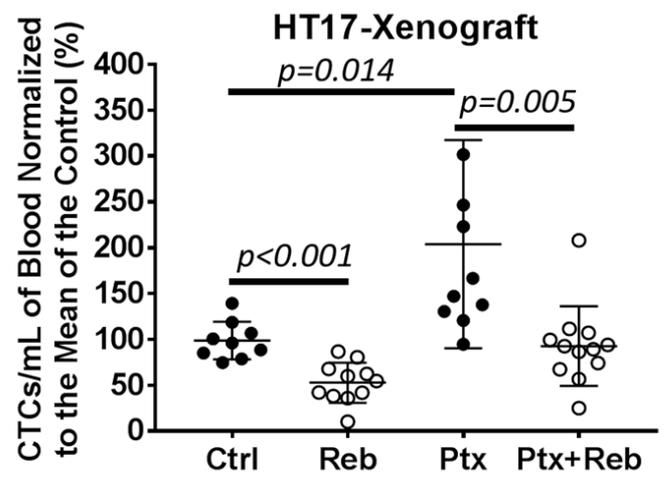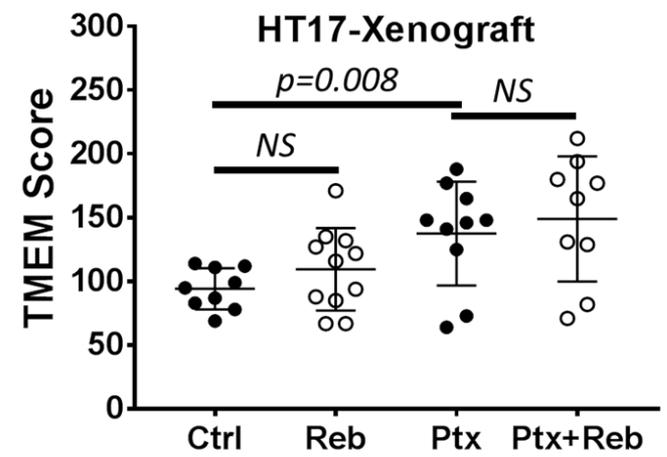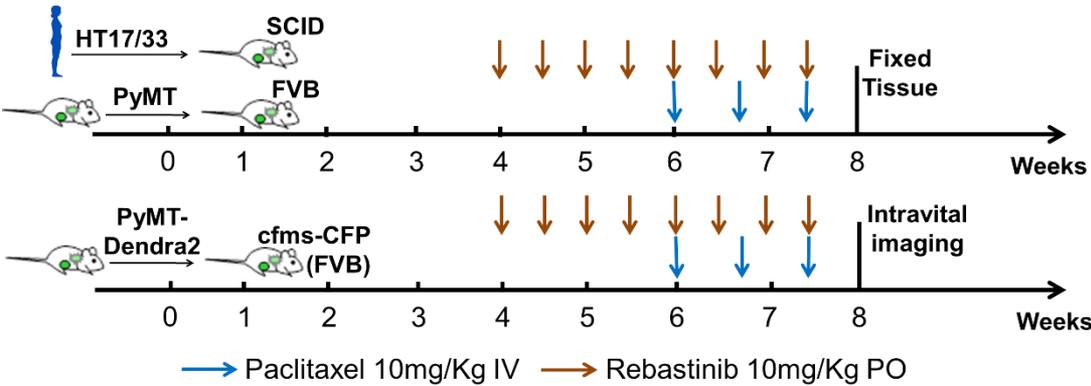
Mice *	Purpose	Ctrl	Reb	Ptx	Ptx+Reb
PyMT-Dendra2/*cfms*-CFP	IVI	-	-	N=12	N=13
PyMT-Spontaneous	Fixed	N=7	N=7	N=7	N=6
HT17 Xenograft	Fixed	N=10	N=12	N=11	N=12

* N of mice corresponds to total number of mice included in the study. When assessing individual variables, the N may vary depending on the exclusion criteria.

Incidence of Bursting (at least 1 event)

Experimental Group	N	%
Paclitaxel	5/12	41.6%
Paclitaxel+Rebastinb	0/13	0%

TMEM-Mena^{INV} Dependent Cancer Cell Dissemination

Karagiannis et al, Sci Trans Med, 2017
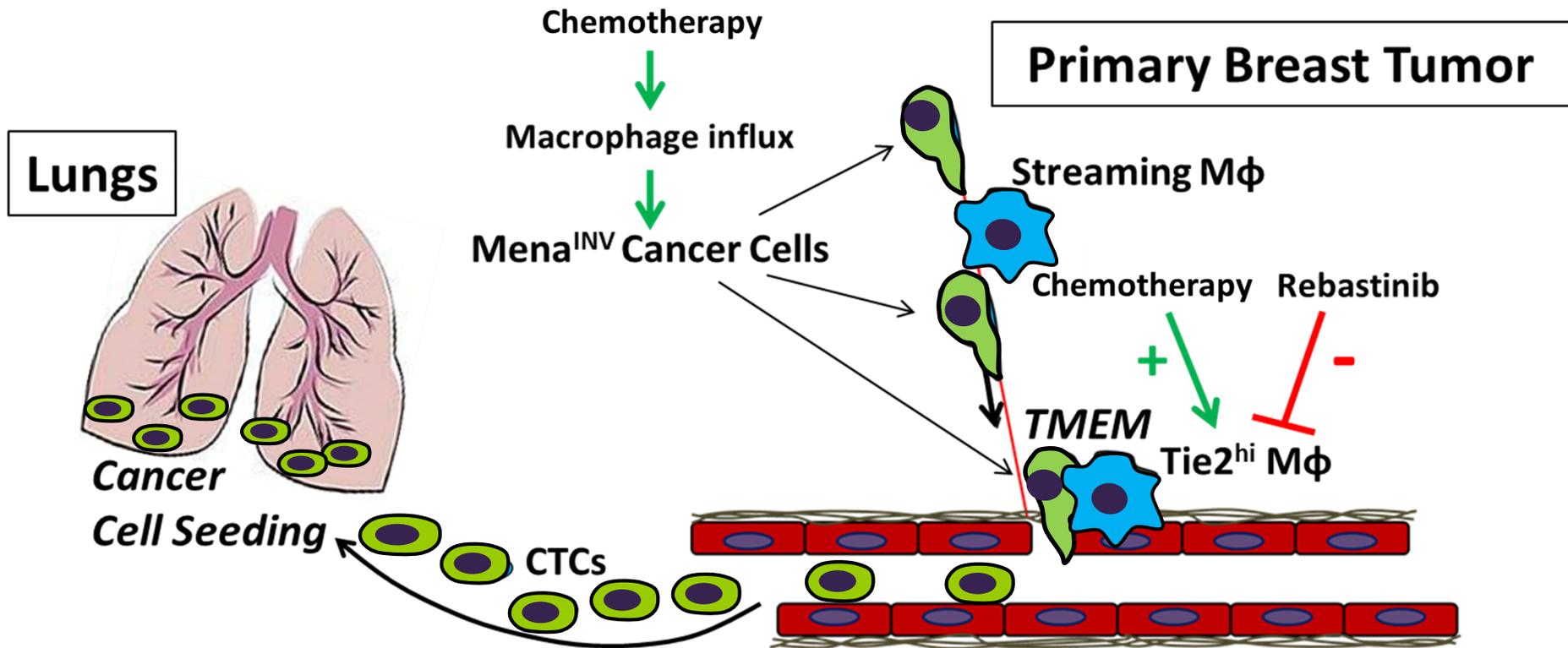
Phase Ib – Study Aims

Joseph Sparano, MD
Professor of Medicine (Oncology)
Professor of Obstetrics,
Gynecology and Women's Health

Jesus Anampa-Mesias, MD
Assistant Professor of
Medicine (Oncology)

- **Aim 1**: To determine the ***overall safety profile and preliminary clinical efficacy of rebastinib*** plus antitubulin therapy (paclitaxel and eribulin) in patients with metastatic HER2- breast cancer.

- **Aim 2**: To evaluate the ***short-term pharmacodynamic effects of rebastinib*** during cycle 1 (3 weeks) of antitubulin therapy +/- rebastinib :
  - Change in Circulating tumor cell (CTCs) assessed by Telomescan method.
  - Correlation between rebastinib plasma concentration and serum angiopoietin (ANG1 and/or ANG2) levels, a surrogate marker for Tie2 inhibition.
  - Effects of rebastinib on circulating Tie-2 expressing monocytes (TEM).

Conclusions

1. Chemotherapy induces macrophage recruitment and tumor cell dissemination in a TMEM and Mena^{INV}-dependent manner.

2. Inhibition of Tie2 on TMEM macrophages with rebastinib inhibits intravasation at TMEM.

3. Rebastinib inhibits tumor cell dissemination in mice and human breast cancer patients causing inhibition of metastasis in mice and potentially in human patients.

4. **The combination of classical chemotherapy with inhibition of microenvironmental contributors to dissemination (e.g. TMEM sites) will be most effective approach for improving long term outcome.**

Acknowledgments

Condeelis/ Oktay Lab:
Javier Cordero
Bojana Gligorijevic
Allison Harney
George Karagiannis
Edison Leung
Antonia Patsialou
Jeanine Pignatelli
Evanthea Roussos
Ved Sharma
Chinmay Surve
Max Weidmann
Jessica Pastoriza
Xiaoming Cheng
Yarong Wang

Einstein Faculty Collaborators:
Aviv Bergman
David Entenberg
Diane Cox
Jeff Polard
Thomas Rohan
Xiaonan Xue
Joseph Sparano
Jesus Anampa Mesias
Joan Jones

Weill-Cornell Pathology:
Brian Robinson
Paula Ginter

MSKCC
Timothy D'Alfonso

Thank you!
Questions?